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Taolin Road, Building 7, Room 201, LuJiaZui Garden,
LuJiaZui, 200135 ShangHai (CN).

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(71) Applicants: **SCHERING CORPORATION** [US/US];
Patent Department - K-6-1 1990, 2000 Galloping Hill
Road, Kenilworth, NJ 07033-0530 (US). **PHARMA-
COPEIA, INC.** [US/US]; 3000 Eastpark Boulevard,
Cranbury, NJ 08512 (US).

(72) Inventors: **TAVERAS, Arthur, G.**; 3 Headley Court,
Denville, NJ 07834 (US). **DWYER, Michael**; 235
Katherine Street, Scotch Plains, NJ 07076 (US). **FER-
REIRA, Johan, A.**; 197 Thunder Circle, Bensalem, PA
19020 (US). **GIRIJAVALLABHAN, Viyyoor, M.**; 10
Maplewood Drive, Parsippany, NJ 07054 (US). **CHAO,
Jianping**; 23 Brainerd Road, Summit, NJ 07901 (US).
BALDWIN, John, J.; 621 Gypsy Hill Circle, Gwynedd
Valley, PA 19437 (US). **MERRITT, J., Robert**; 14
Gloucester Lane, Ewing, NJ 08618 (US). **LI, Ge**; 815

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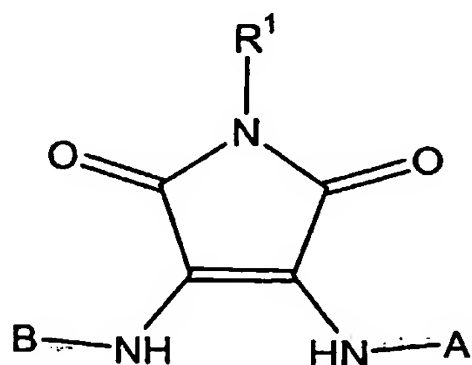
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(54) Title: 3,4-DI-SUBSTITUTED MALEIMIDE COMPOUNDS AS CXC-CHEMOKINE RECEPTOR ANTAGONISTS



(I)

(57) Abstract: Disclosed are compounds of the formula (I) or a phar-
maceutically acceptable salt or solvate thereof. The compounds are use-
ful for the treatment of chemokine-mediated diseases such as acute and
chronic inflammatory disorders and cancer.

WO 03/031440 A1

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**3,4 -Di-SUBSTITUTED MALEIMIDE COMPOUNDS
AS CXC CHEMOKINE RECEPTOR ANTAGONISTS**

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FIELD OF THE INVENTION

The present invention relates to novel substituted maleimide compounds, pharmaceutical compositions containing the compounds, and the use of the compounds in treating CXC chemokine-mediated diseases.

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BACKGROUND OF THE INVENTION

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Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T-cells, eosinophils, basophils, neutrophils and endothelial cells to sites of inflammation and tumor growth. There are two main classes of chemokines, the CXC-chemokines and the CC- chemokines. The class depends on whether the first two cysteines are separated by a single amino acid (CXC-chemokines) or are adjacent (CC-chemokines). The CXC-chemokines include interleukin-8 (IL-8), neutrophil-activating protein-1 (NAP-1), neutrophil-activating protein-2 (NAP-2), GRO α , GRO β , GRO γ , ENA-78, GCP-2, IP-10, MIG and PF4. CC chemokines include RANTES, MIP -1 α , MIP-2 β , monocyte chemotactic protein-1 (MCP-1), MCP-2, MCP-3 and eotaxin. Individual members of the chemokine families are known to be bound by at least one chemokine receptor, with CXC-chemokines generally bound by members of the CXCR class of receptors, and CC-chemokines by members of the CCR class of receptors. For example, IL-8 is bound by the CXCR-1 and CXCR-2 receptors.

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Since CXC-chemokines promote the accumulation and activation of neutrophils, these chemokines have been implicated in a wide range of acute and chronic inflammatory disorders including psoriasis and rheumatoid arthritis. Baggiolini et al., FEBS Lett. 307, 97 (1992); Miller et al., Crit. Rev. Immunol. 12, 17

(1992); Oppenheim et al., *Annu. Rev. Immunol.* 9, 617 (1991); Seitz et al., *J. Clin. Invest.* 87, 463 (1991); Miller et al., *Am. Rev. Respir. Dis.* 146, 427 (1992); Donnelly et al., *Lancet* 341, 643 (1993).

ELRCXC chemokines including IL-8, GRO α , GRO β , GRO γ , NAP-2, and
5 ENA-78 (Strieter et al. 1995 *JBC* 270 p. 27348-57) have also been implicated in the
induction of tumor angiogenesis (new blood vessel growth). All of these
chemokines are believed to exert their actions by binding to the 7 transmembrane
G-protein coupled receptor CXCR2 (also known as IL-8RB), while IL-8 also binds
CXCR1 (also known as IL-8RA). Thus, their angiogenic activity is due to their
10 binding to and activation of CXCR2, and possible CXCR1 for IL-8, expressed on the
surface of vascular endothelial cells (ECs) in surrounding vessels.

Many different types of tumors have been shown to produce ELRCXC
chemokines and their production has been correlated with a more aggressive
phenotype (Inoue et al. 2000 *Clin Cancer Res* 6 p. 2104-2119) and poor prognosis
15 (Yoneda et al. 1998 *J Nat Cancer Inst* 90 p. 447-454). Chemokines are potent
chemotactic factors and the ELRCXC chemokines have been shown to induce EC
chemotaxis. Thus, these chemokines probably induce chemotaxis of endothelial
cells toward their site of production in the tumor. This may be a critical step in the
induction of angiogenesis by the tumor. Inhibitors of CXCR2 or dual inhibitors of
20 CXCR2 and CXCR1 will inhibit the angiogenic activity of the ELRCXC chemokines
and therefore block the growth of the tumor. This anti-tumor activity has been
demonstrated for antibodies to IL-8 (Arenberg et al. 1996 *J Clin Invest* 97 p. 2792-
2802), ENA-78 (Arenberg et al. 1998 *J Clin Invest* 102 p. 465-72), and GRO α
(Haghnegahdar et al. *J. Leukoc Biology* 2000 67 p. 53-62).

25 Many tumor cells have also been shown to express CXCR2 and thus tumor
cells may also stimulate their own growth when they secrete ELRCXC chemokines.
Thus, along with decreasing angiogenesis, inhibitors of CXCR2 may directly inhibit
the growth of tumor cells.

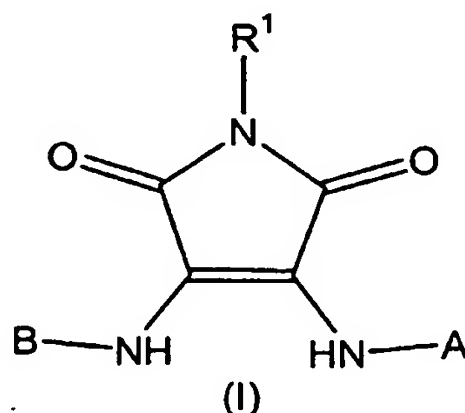
Hence, the CXC-chemokine receptors represent promising targets for the
30 development of novel anti-inflammatory and anti-tumor agents.

There remains a need for compounds that are capable of modulating activity
at CXC-chemokine receptors. For example, conditions associated with an increase
in IL-8 production (which is responsible for chemotaxis of neutrophil and T-cell

subsets into the inflammatory site and growth of tumors) would benefit by compounds that are inhibitors of IL-8 receptor binding.

Summary of the Invention

5 The present invention provides novel compounds represented by the formula (I):



10 or a pharmaceutically acceptable salt or solvate thereof, wherein R¹, A and B are defined below.

 This invention also provides a method of treating an α -chemokine mediated disease in a mammal which comprises administering to a patient in need thereof of a therapeutically effective amount of at least one (usually 1) compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

15 This invention also provides a method treating a chemokine-mediated disease wherein the chemokine binds to a CXCR2 and/or CXCR1 receptor in a mammal, which comprises administering to a patient in need thereof a therapeutically effective amount of at least one (usually one) compound of formula I

20 This invention also provides a method of treating a chemokine-mediated disease wherein the chemokine binds to a CXC receptor in a mammal, which comprises administering to a patient in need thereof a therapeutically effective amount of at least one (usually one) compound of formula I.

25 This invention also provides a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (usually 1) compound of formula I.

 This invention also provides a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (usually 1) compound of formula I, and administering at least one known anti-cancer agent and/or radiation therapy.

This invention also provides a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (usually 1) compound of formula I, and administering at least one known anti-cancer agent and/or radiation therapy, wherein said anti-cancer agent is selected from the group consisting of alkylating agents, antimetabolites, natural products and their derivatives, hormones, anti-hormones, anti-angiogenic agents and steroids (including synthetic analogs), and synthetics.

This invention also provides a method of treating cancer, comprising administering to a patient in need thereof, concurrently or sequentially, a therapeutically effective amount of (a) at least one (usually 1) compound of formula (I), and (b) at least one anticancer agent selected from the group consisting of: microtubule affecting agents, antineoplastic agents, anti-angiogenesis agents, VEGF receptor kinase inhibitors, antibodies against the VEGF receptor, interferon, and radiation.

This invention also provides a method of treating cancer in a patient in need of such treatment comprising administering to said patient at least one (usually 1) compound of formula I in combination with at least one (usually 1) antineoplastic agent selected from the group consisting of: gemcitabine, paclitaxel (Taxol®), 5-Fluorouracil (5-FU), cyclophosphamide (Cytosan®), temozolomide, and Vincristine.

This invention also provides a method of treating cancer, comprising administering, concurrently or sequentially, an effective amount of (a) at least one (usually 1) compound of formula (I), and (b) a microtubule affecting agent (e.g., paclitaxel).

This invention also provides a method treating cancer in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of: (a) at least one (usually 1) compound of formula I concurrently or sequentially with (b) at least one (usually 1) agent selected from the group consisting of: (1) antineoplastic agents, (2) microtubule affecting agents, and (3) anti-angiogenesis agents.

This invention also provides a method of inhibiting angiogenesis in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (usually 1) compound of formula I.

This invention also provides a method of inhibiting angiogenesis in a patient in need of such treatment comprising administering to said patient an effective

amount of at least one (usually 1) compound of formula I, wherein the tumor type is melanoma, gastric carcinoma or non-small cell lung carcinoma.

This invention also provides a method of inhibiting angiogenesis in a patient in need of such treatment comprising administering to said patient an effective
5 amount of at least one (usually 1) compound of formula I, and administering at least one known anti-cancer agent and/or radiation therapy.

This invention also provides a method of inhibiting angiogenesis in a patient in need of such treatment comprising administering to said patient an effective
10 amount of at least one (usually 1) compound of formula I, and administering at least one known anti-cancer agent and/or radiation therapy, wherein said anti-cancer agent is selected from the group consisting of alkylating agents, antimetabolites, natural products and their derivatives, hormones, anti-hormones, anti-angiogenic agents and steroids (including synthetic analogs), and synthetics.

This invention also provides a method of inhibiting angiogenesis in a patient
15 in need of such treatment comprising administering to said patient an effective amount of at least one (usually 1) compound of formula I, and administering at least one known anti-cancer agent and/or radiation therapy, wherein said anti-cancer agent is selected from the group consisting of alkylating agents, antimetabolites, natural products and their derivatives, hormones, anti-hormones, anti-angiogenic
20 agents and steroids (including synthetic analogs), and synthetics, wherein said anti-angiogenic agent is selected from the group consisting of Marimastat, AG3340, Col-3, Neovastat, BMS-275291, Thalidomide, Squalamine, Endostatin, SU-5416, SU-6668, Interferon-alpha, Anti-VEGF antibody, EMD121974, CAI, Interleukin-12, IM862, Platelet Factor-4, Vitaxin, Angiostatin, Suramin, TNP-470, PTK-787, ZD-6474, ZD-101, Bay 129566, CGS27023A, VEGF receptor kinase inhibitors, taxotere
25 and Taxol.

This invention also provides a method of inhibiting angiogenesis in a patient in need of such treatment comprising administering to said patient an effective
30 amount of at least one (usually 1) compound of formula I, and administering at least one known anti-angiogenesis compound.

This invention also provides a method of inhibiting angiogenesis in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (usually 1) compound of formula I, and administering at least one known anti-angiogenesis compound, wherein said known anti-angiogenesis

compound is selected from the group consisting of Marimastat, AG3340, Col-3, Neovastat, BMS-275291, Thalidomide, Squalamine, Endostatin, SU-5416, SU-6668, Interferon-alpha, Anti-VEGF antibody, EMD121974, CAI, Interleukin-12, IM862, Platelet Factor-4, Vitaxin, Angiostatin, Suramin, TNP-470, PTK-787, ZD-6474, ZD-101, Bay 129566, CGS27023A, VEGF receptor kinase inhibitors, taxotere and Taxol.

This invention also provides a method of treating a disease selected from the group consisting of gingivitis, respiratory viruses, herpes viruses, hepatitis viruses, HIV, kaposi's sarcoma associated virus and atherosclerosis in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually one) compound of formula I.

This invention also provides a method of treating angiogenic ocular disease (e.g., ocular inflammation (e.g., Uveitis), retinopathy of prematurity, diabetic retinopathy, macular degeneration with the wet type preferred and corneal neovascularization) in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (usually 1) compound of formula I.

This invention also provides a method of treating a disease selected from the group consisting of: psoriasis, atopic dermatitis, asthma, COPD, adult respiratory disease, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, stroke, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer's disease, graft vs. host reaction, allograft rejections, malaria, acute respiratory distress syndrome, delayed type hypersensitivity reaction, atherosclerosis, cerebral and cardiac ischemia, osteoarthritis, multiple sclerosis, restinosis, angiogenesis, osteoporosis, gingivitis, respiratory viruses, herpes viruses, hepatitis viruses, HIV (i.e., AIDS), Kaposi's sarcoma associated virus, meningitis, cystic fibrosis, pre-term labor, cough, pruritis, multi-organ dysfunction, trauma, strains, sprains, contusions, psoriatic arthritis, herpes, encephalitis, CNS vasculitis, traumatic brain injury, CNS tumors, subarachnoid hemorrhage, post surgical trauma, interstitial pneumonitis, hypersensitivity, crystal induced arthritis, acute and chronic pancreatitis, acute alcoholic hepatitis, necrotizing enterocolitis, chronic sinusitis, angiogenic ocular disease, ocular inflammation, retinopathy of prematurity, diabetic retinopathy, macular degeneration with the wet type preferred and corneal neovascularization,

polymyositis, vasculitis, acne, gastric and duodenal ulcers, celiac disease, esophagitis, glossitis, airflow obstruction, airway hyperresponsiveness, bronchiectasis, bronchiolitis, bronchiolitis obliterans, chronic bronchitis, cor pulmonae, cough, dyspnea, emphysema, hypercapnea, hyperinflation, hypoxemia, hyperoxia-induced inflammations, hypoxia, surgical lung volume reduction, pulmonary fibrosis, pulmonary hypertension, right ventricular hypertrophy, peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD), granulocytic ehrlichiosis, sarcoidosis, small airway disease, ventilation-perfusion mismatching, wheeze, colds, gout, alcoholic liver disease, lupus, burn therapy, periodontitis, transplant reperfusion injury and early transplantation in a patient in need of such treatment comprising administering to said patient an effective amount of at least one compound (usually 1) of formula I.

This invention also provides a method of treating a chemokine (i.e., a CXC chemokine) mediated disease in a patient in need of such treatment comprising administering to said patient at least one (usually 1) compound of formula I in combination with at least one (usually 1) other medicament (e.g., a drug, agent or therapeutic) useful for the treatment of chemokine mediated diseases.

This invention also provides a method of treating a chemokine mediated disease in a patient in need of such treatment comprising administering to said patient at least one (usually 1) compound of formula I in combination with at least one (usually 1) other medicament (e.g., a drug, agent or therapeutic) selected from the group consisting of:

- a) disease modifying antirheumatic drugs;
- b) nonsteroidal anitflammatory drugs;
- c) COX-2 selective inhibitors;
- d) COX-1 inhibitors;
- e) immunosuppressives;
- f) steroids;
- g) biological response modifiers; and
- h) other anti-inflammatory agents or therapeutics useful for the treatment of chemokine mediated diseases.

This invention also provides a method of treating a pulmonary disease (e.g., COPD asthma or cystic fibrosis) in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one

compound (usually 1) of formula I; in combination with at least one (usually 1) compound selected from the group consisting of: glucocorticoids, 5-lipoxygenase inhibitors, β -2 adrenoceptor agonists, muscarinic M1 antagonists, muscarinic M3 antagonists, muscarinic M2 agonists, NK3 antagonists, LTB4 antagonists, cysteinyl leukotriene antagonists, bronchodilators, PDE4 inhibitors, PDE inhibitors, elastase inhibitors, MMP inhibitors, phospholipase A2 inhibitors, phospholipase D inhibitors, histamine H1 antagonists, histamine H3 antagonists, dopamine agonists, adenosine A2 agonists, NK1 and NK2 antagonists, GABA-b agonists, nociceptin agonists, expectorants, mucolytic agents, decongestants, antioxidants, anti-IL-8 anti-bodies, anti-IL-5 antibodies, anti-IgE antibodies, anti-TNF antibodies, IL-10, adhesion molecule inhibitors, and growth hormones.

This invention also provides a method of treating multiple sclerosis in a patient in need of such treatment comprising administering to said patient, a therapeutically effective amount of at least one (usually 1) compound of formula I in combination with at least one compound selected from the group consisting of glatiramer acetate, glucocorticoids, methotrexate, azothioprine, mitoxantrone, chemokine inhibitors, and CB2-selective inhibitors.

This invention also provides a method of treating multiple sclerosis in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually 1) compound of formula I, in combination with at least one compound selected from the group consisting of: methotrexate, cyclosporin, leflunimide, sulfasalazine, β -methasone, β -interferon, glatiramer acetate, prednisone, etanercept, and infliximab.

This invention also provides a method of treating rheumatoid arthritis in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually 1) compound of formula I in combination with at least one compound selected from the group consisting of COX-2 inhibitors, COX inhibitors, immunosuppressives (e.g., methotrexate, cyclosporin, leflunimide and sulfasalazine), steroids (e.g., betamethasone, cortisone and dexamethasone), PDE IV inhibitors, anti-TNF- α compounds, MMP inhibitors, glucocorticoids, chemokine inhibitors, CB2-selective inhibitors, and other classes of compounds indicated for the treatment of rheumatoid arthritis.

This invention also provides a method of treating stroke and cardiac reperfusion injury in a patient in need of such treatment comprising administering to

said patient a therapeutically effective amount of at least one compound (usually 1) of formula I in combination with at least one compound selected from the group consisting of thrombolytics (e.g., tenecteplase, TPA, alteplase), antiplatelet agents (e.g., gpIIb/IIIa), antagonists (e.g., abciximab and eptifibatide), anticoagulants (e.g., heparin), and other compounds indicated for the treatment of rheumatoid arthritis.

This invention also provides a method of treating stroke and cardiac reperfusion injury in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually 1) compound of formula I in combination with at least one compound selected from the group consisting of tenecteplase, TPA, alteplase, abciximab, eptifibatide, and heparin.

This invention also provides a method of treating psoriasis in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of at least one (usually 1) compound of formula I in combination with at least one compound selected from the group consisting of immunosuppressives (e.g., methotrexate, cyclosporin, leflunimide and sulfasalazine), steroids (e.g., β -methasone) and anti-TNF- α compounds (e.g., etanercept and infliximab).

This invention also provides a pharmaceutical composition comprising at least one (usually 1) compound of formula I and a pharmaceutically acceptable carrier.

This invention also provides a pharmaceutical composition comprising at least one (usually 1) compound of formula I, and at least one (usually 1) other agent, medicament, antibody and/or inhibitor disclosed above, and a pharmaceutically acceptable carrier.

Detailed Description of the Preferred Embodiments

Unless indicated otherwise, the following definitions apply throughout the present specification and claims. These definitions apply regardless of whether a term is used by itself or in combination with other terms. Hence the definition of "alkyl" applies to "alkyl" as well as to the "alkyl" portions of "alkoxy", etc.

When any variable (e.g., aryl, R^2) occurs more than one time in any constituent, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

"An effective amount" means a therapeutically acceptable amount (i.e., that amount which provides the desired therapeutic effective).

"At least one" means one or more (e.g., 1-3, 1-2, or 1).

5 "Composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

10 "In combination with" as used to describe the administration of a compound of formula I with other medicaments in the methods of treatment of this invention, means that the compounds of formula I and the other medicaments are administered sequentially or concurrently in separate dosage forms, or are administered concurrently in the same dosage form.

"Mammal" includes a human being, and preferably means a human being.

"One or more" means at least one (e.g., 1-3, 1-2 or 1).

"Patient" includes both human and other mammals, preferably human.

15 "Prodrug" represents compounds which are rapidly transformed *in vivo* to the parent compound of the above formula, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

"Alkyl" means a straight or branched saturated hydrocarbon chain having 1 to 20 carbon atoms, preferably 1 to 12 carbon atoms, more preferably 1 to 6 carbon atoms.

25 "Alkoxy" means an alkyl-O- group wherein alkyl is as defined above. Non-limiting examples of alkoxy groups include: methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen.

30 "Alkenyl" means a straight or branched aliphatic hydrocarbon group having at least one carbon-carbon double bond, and 2 to 20 carbon atoms, preferably 2 to 12 carbon atoms, and more preferably 2 to 6 carbon atoms. Non-limiting examples of alkenyl groups include: ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl.

"Alkynyl" means a straight or branched aliphatic hydrocarbon group having at least one carbon-carbon triple bond, and 2 to 15 carbon atoms, preferably 2 to 12

carbon atoms, and more preferably 2 to 4 carbon atoms. Non-limiting examples of alkynyl groups include ethynyl, propynyl, 2-butylnyl, 3-methylbutynyl, n-pentylnyl, and decynyl.

5 "Aryl" means an aromatic monocyclic or multicyclic ring system, wherein at least one ring is aromatic, comprising about 6 to about 14 carbon atoms, and preferably about 6 to about 10 carbon atoms. Non-limiting examples of suitable aryl groups include: phenyl, naphthyl, indenyl, tetrahydronaphthyl, indanyl, anthracenyl, and fluorenyl. The aryl group can be unsubstituted or substituted with one, two, or three substituents independently selected from the group consisting of: lower alkyl, 10 halo, cyano, nitro, haloalkyl, hydroxy, alkoxy, carboxy, carboxyalkyl, carboxamide, mercapto, sulfhydryl, amino, alkylamino, dialkylamino, sulfonyl, sulfonamido, aryl and heteroaryl.

"Arylalkyl" means an aryl group, as defined above, bound to an alkyl group, as defined above, wherein the alkyl group is bound to the parent moiety. Non- 15 limiting examples of suitable arylalkyl groups include benzyl, phenethyl and naphthleneylmethyl.

"Cycloalkyl" means saturated carbocyclic rings having 3 to 10 (e.g., 3 to 7) carbon atoms, preferably 5 to 10 carbon atoms, and more preferably 5 to 7 carbon atoms, and having one to three rings. Non-limiting examples of cycloalkyl groups 20 include: cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and adamantyl.

"Cycloalkylalkyl" means a cycloalkyl group bound to the parent moiety through an alkyl group. Non-limiting examples include: cyclopropylmethyl and cyclohexylmethyl.

25 "Cycloalkenyl" means a non-aromatic mono or multicyclic ring system comprising 3 to 10 carbon atoms, and preferably 5 to 10 carbon atoms, and having at least one carbon-carbon double bond. Preferred cycloalkenyl rings have 5 to 7 carbon atoms. Non-limiting examples of cycloalkyl groups include cyclopentenyl, cyclohexenyl, cycloheptenyl, and norbornenyl.

30 "Fluoroalkyl" represents a straight or branched saturated hydrocarbon chain (e.g., a carbon chain comprising 1-20 carbon atoms), substituted with one or more fluorine atoms.

"Halo" means fluoro, chloro, bromo, or iodo groups.

"Haloalkyl" means an alkyl group as defined above wherein one or more hydrogen atoms on the alkyl is replaced by a halo group defined above.

"Halogen" means fluorine, chlorine, bromine or iodine.

"Heteroaryl" refers to a 5 to 14, preferably 5 to 10 membered single or benzofused aromatic rings consisting of 1 to 3 heteroatoms independently selected from the group consisting of -O-, -S, and -N=, provided that the rings do not possess adjacent oxygen and/or sulfur atoms. Preferred heteroaryls contain 5 to 6 ring atoms. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. The heteroaryl group can be unsubstituted or substituted with one, two, or three substituents independently selected from lower alkyl, halo, cyano, nitro, haloalkyl, hydroxy, alkoxy, carboxy, carboxyalkyl, carboxamide, sulfhydryl, amino, alkylamino and dialkylamino. Non-limiting examples of heteroaryls include: pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalynyl, phthalazinyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolynyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolynyl, benzoazaindolyl, 1,2,4-triazinyl, and benzothiazolyl.

"Heteroarylalkyl" means a heteroaryl group, as defined above, bound to an alkyl group, as defined above, where the bond to the parent moiety is through the alkyl group.

"Heterocyclic acidic functional group" is intended to include groups such as, pyrrole, imidazole, triazole, tetrazole, and the like.

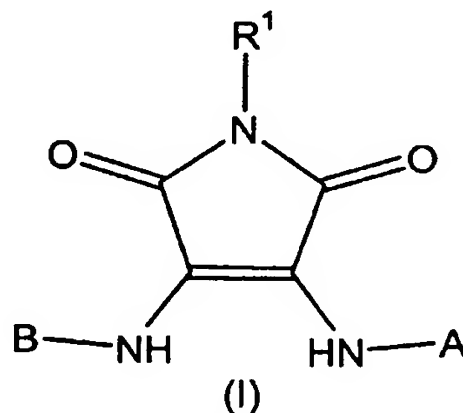
"Heterocyclyl" or "heterocyclic" or "heterocycloalkyl" means a non-aromatic saturated monocyclic or multicyclic ring system (i.e., a saturated carbocyclic ring or ring system) comprising 3 to 10 ring atoms (e.g., 3 to 7 ring atoms), preferably 5 to 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls have 5 to 6 ring atoms. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Examples include, but are not limited to: oxirane, oxetanyl, tetrahydropyridinyl, tetrahydropyrimidinyl, hydantoin, valerolactam, pyrrolidinone, piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-

dioxolanyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, and tetrahydrothiopyranyl.

N-oxides can form on a tertiary nitrogen present in an R substituent, or on =N- in a heteroaryl ring substituent and are included in the compounds of formula (I).

The following solvents and reagents are referred to herein by the abbreviations indicated: tetrahydrofuran (THF); ethanol (EtOH); methanol (MeOH); acetic acid (HOAc or AcOH); ethyl acetate (EtOAc); N,N-dimethylformamide (DMF); trifluoroacetic acid (TFA); trifluoroacetic anhydride (TFAA); 1-hydroxybenzotriazole (HOBT); m-chloroperbenzoic acid (MCPBA); triethylamine (Et₃N); diethyl ether (Et₂O); ethyl chloroformate (ClCO₂Et); and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (DEC).

The novel compounds of this invention are represented by the formula (I):



or a pharmaceutically acceptable salt or solvate thereof:

R¹ is selected from H, aryl, heteroaryl, alkyl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, and heterocycloalkylalkyl optionally substituted with one or more substituents selected from the group consisting of:

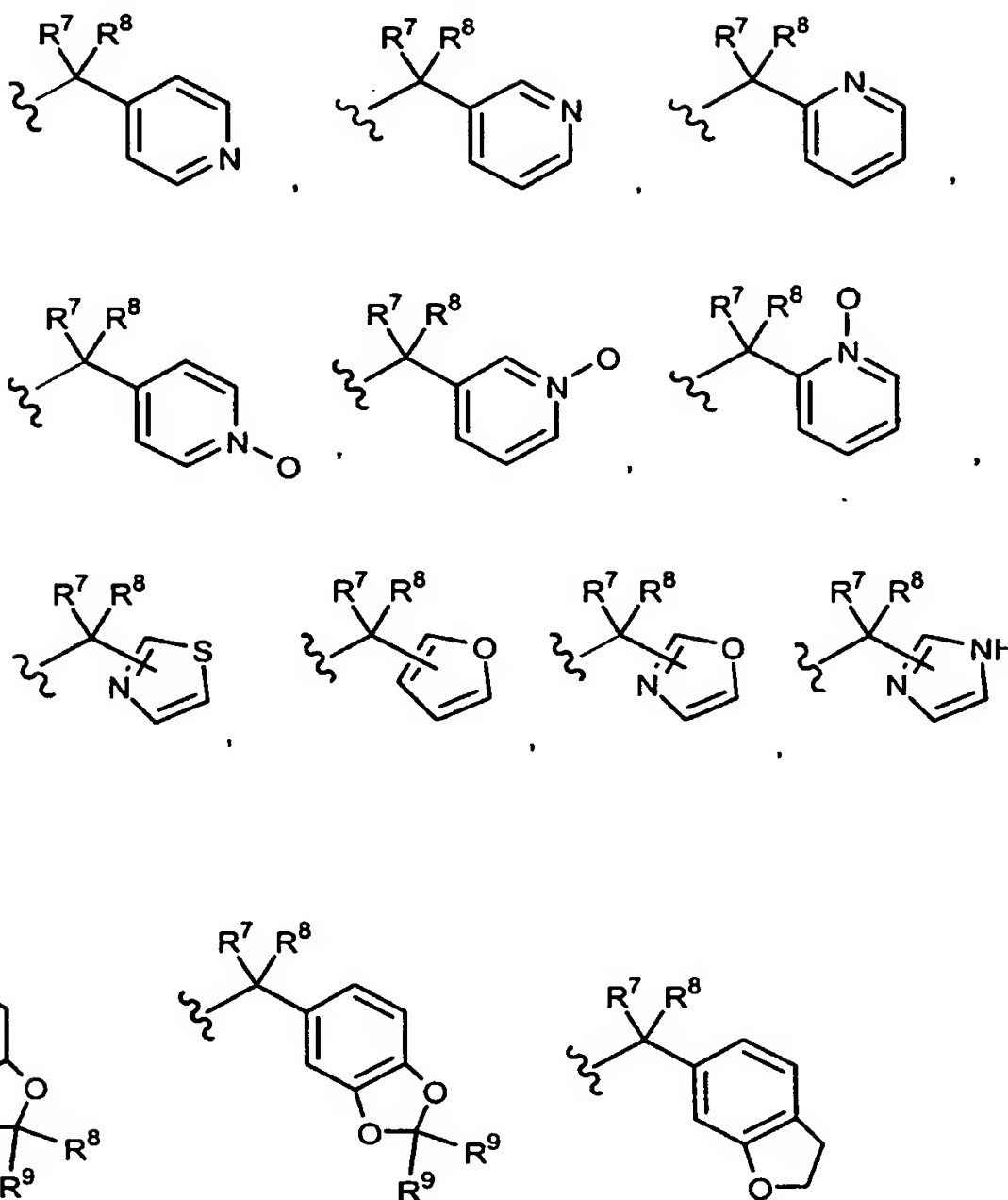
- a) H,
- b) halogen,
- c) -CF₃,
- d) -COR¹³,
- e) -OH,
- f) -NR¹³R¹⁴,
- g) -NO₂,
- h) cyano,
- i) -SO₂OR¹³,
- j) -Si(alkyl),

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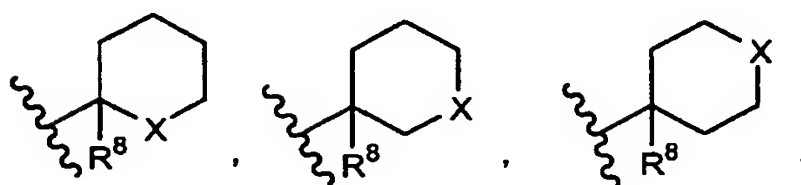
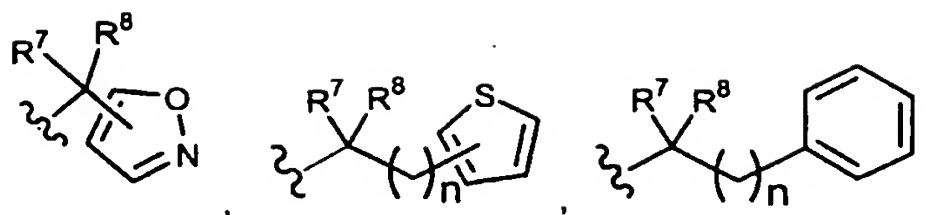
- k) $-\text{Si}(\text{aryl})$,
l) $-\text{CO}_2\text{R}^{13}$,
m) $-\text{CONR}^{13}\text{R}^{14}$,
n) $-\text{SO}_2\text{NR}^{13}\text{R}^{14}$,
o) $-\text{SO}_2\text{R}^{13}$,
p) $-\text{OR}^{13}$,
q) $-\text{NR}^{13}\text{R}^{14}$,
r) $-\text{O}(\text{C}=\text{O})\text{R}^{13}$,
s) $-\text{O}(\text{C}=\text{O})\text{NR}^{13}\text{R}^{14}$,
t) $-\text{NR}^{13}\text{COR}^{14}$ and
u) $-\text{NR}^{13}\text{CO}_2\text{R}^{14}$;

A is selected from the group consisting of:

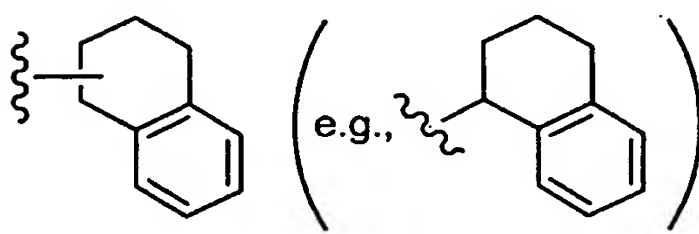
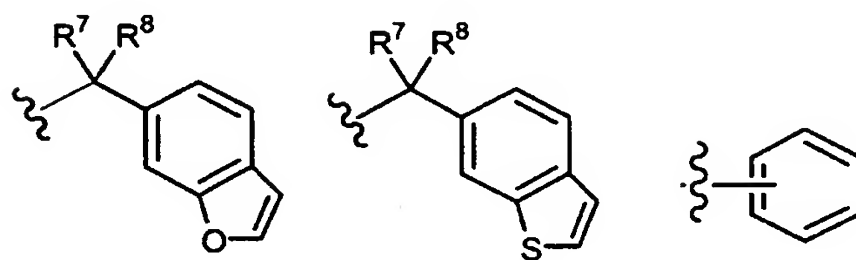
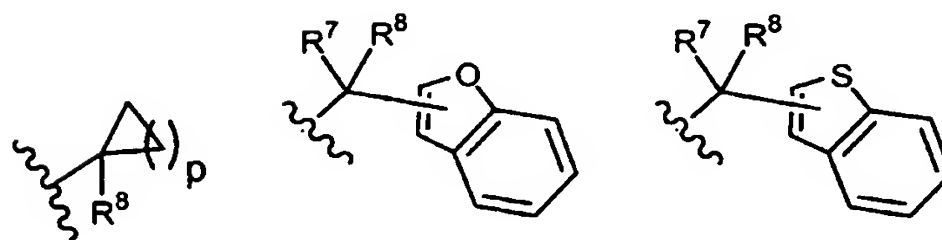
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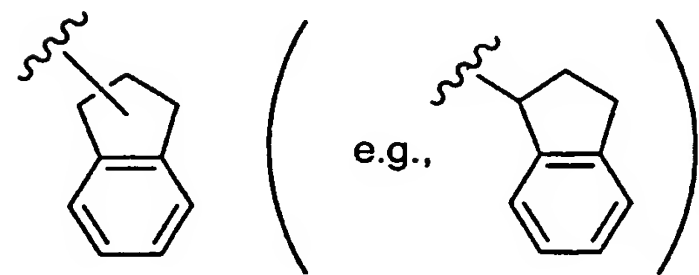
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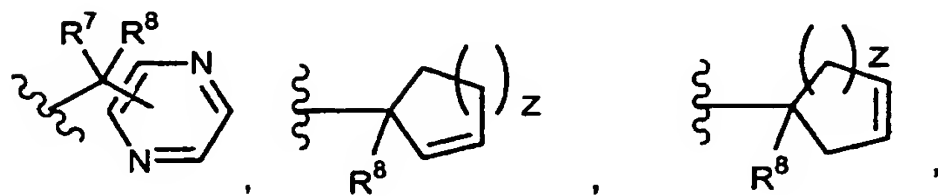
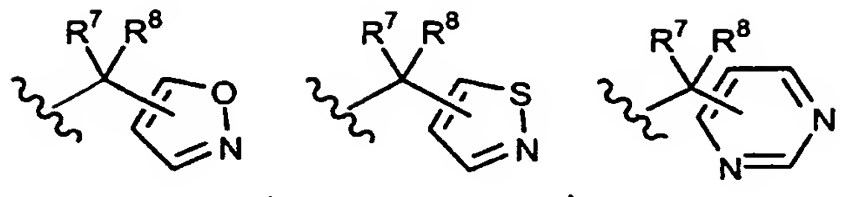
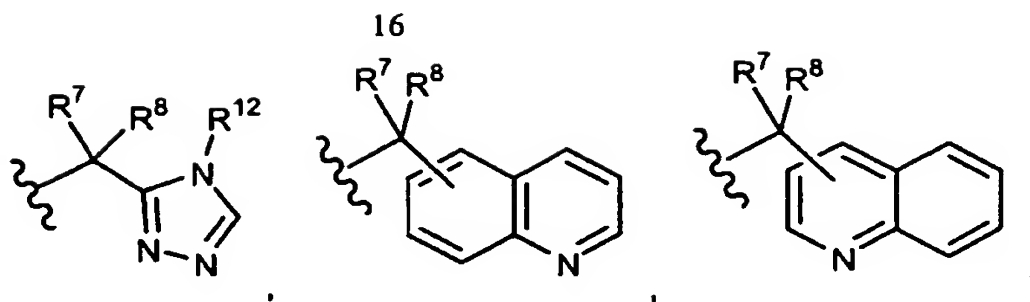


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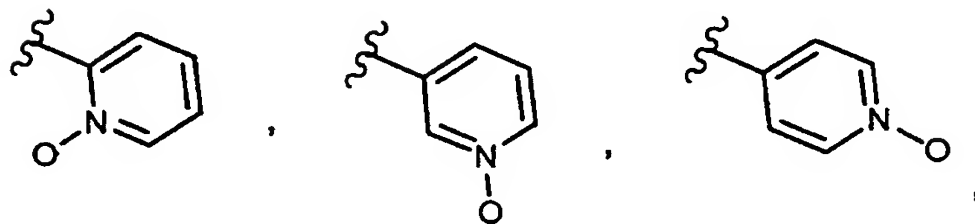
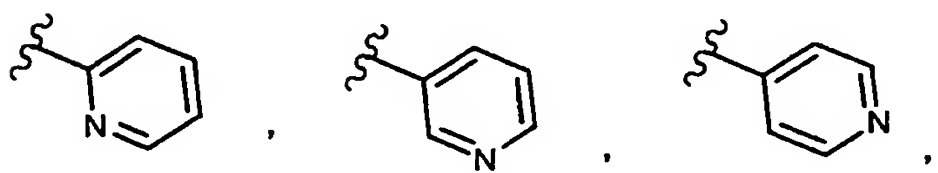


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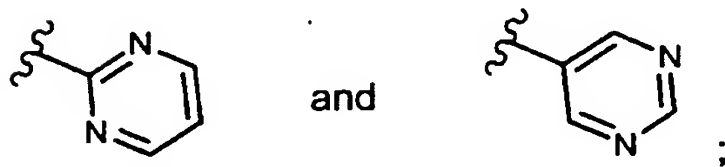




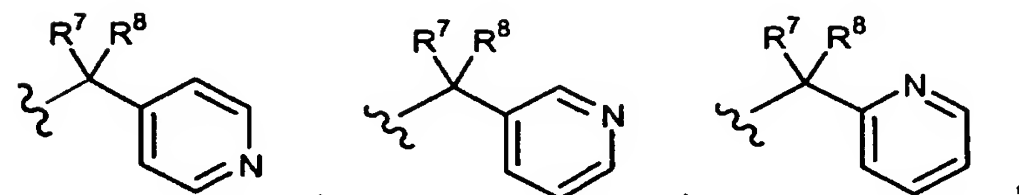
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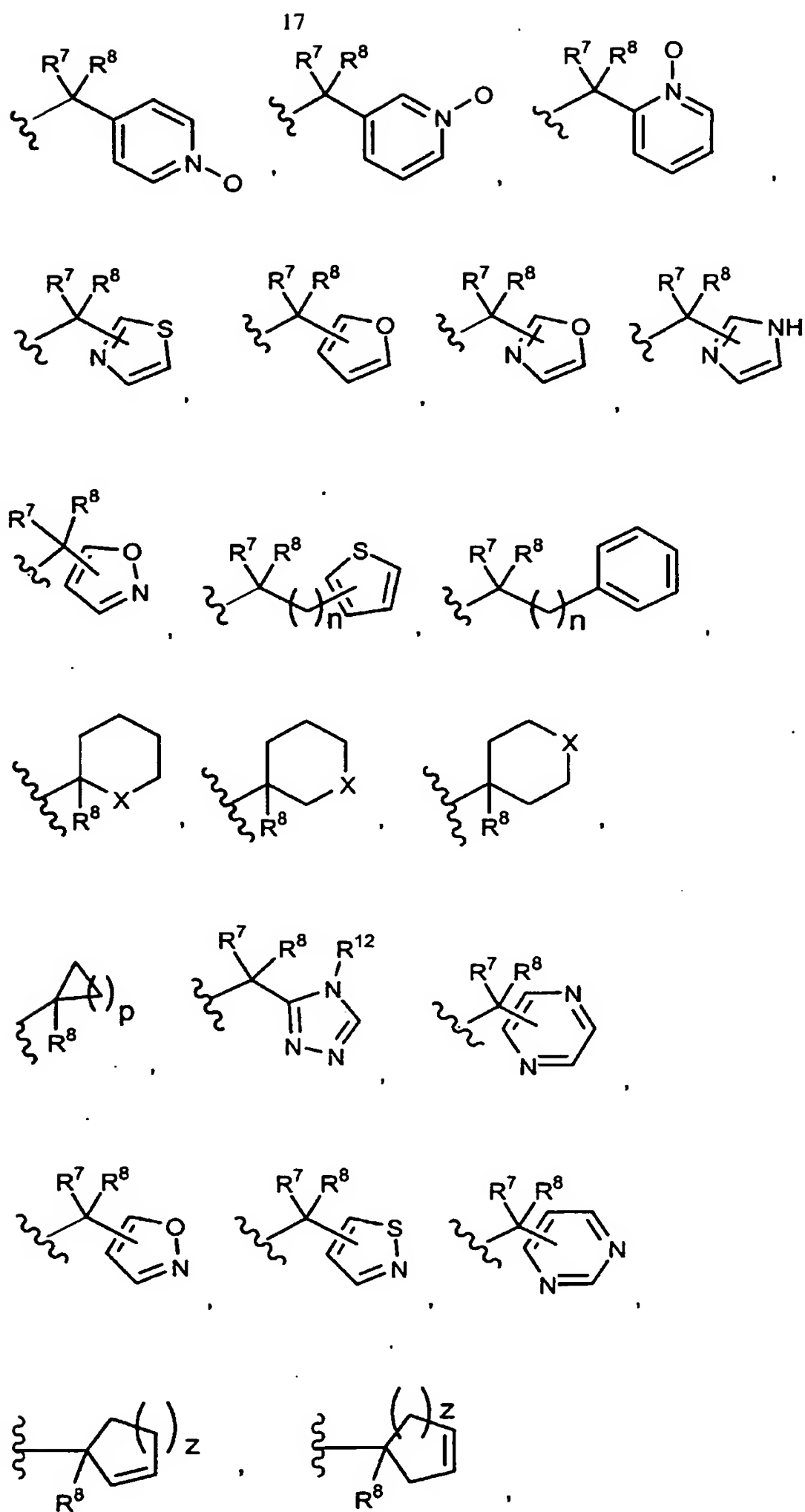
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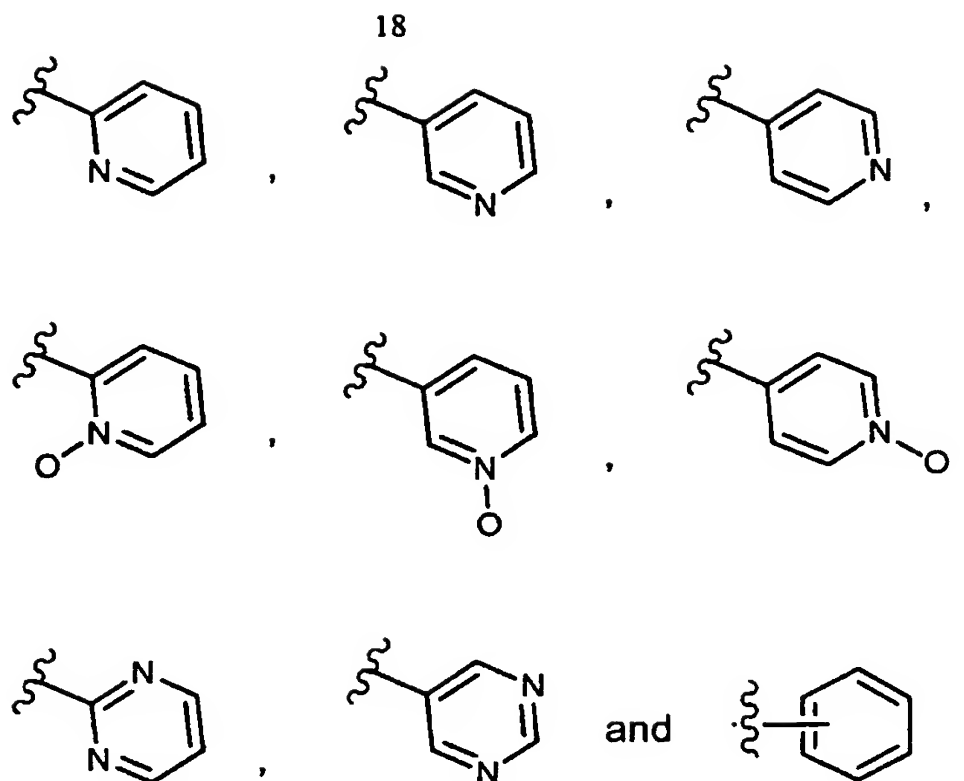
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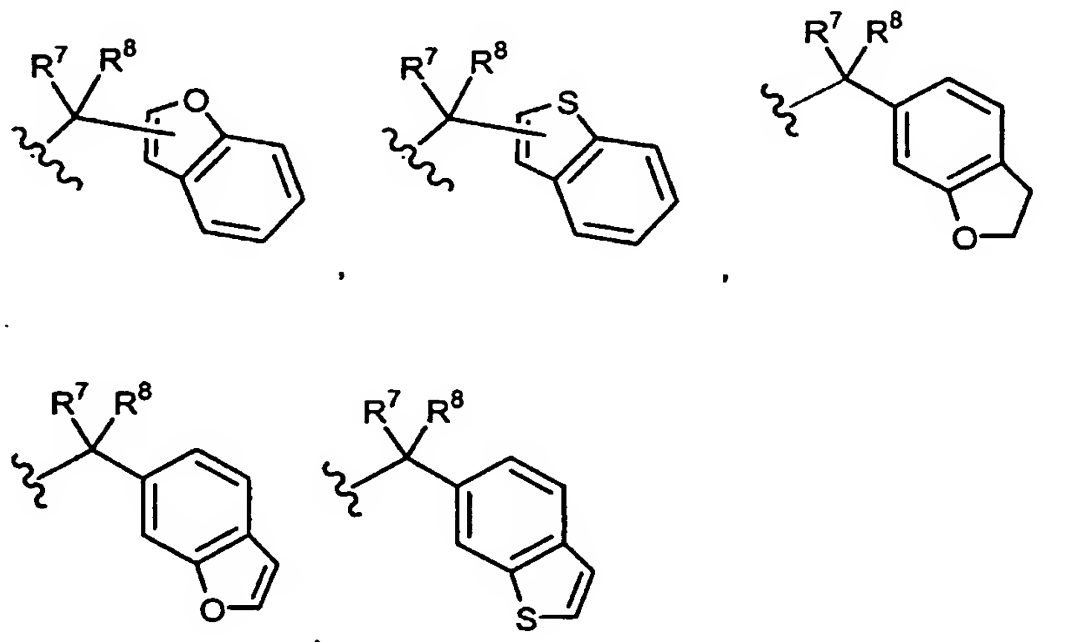
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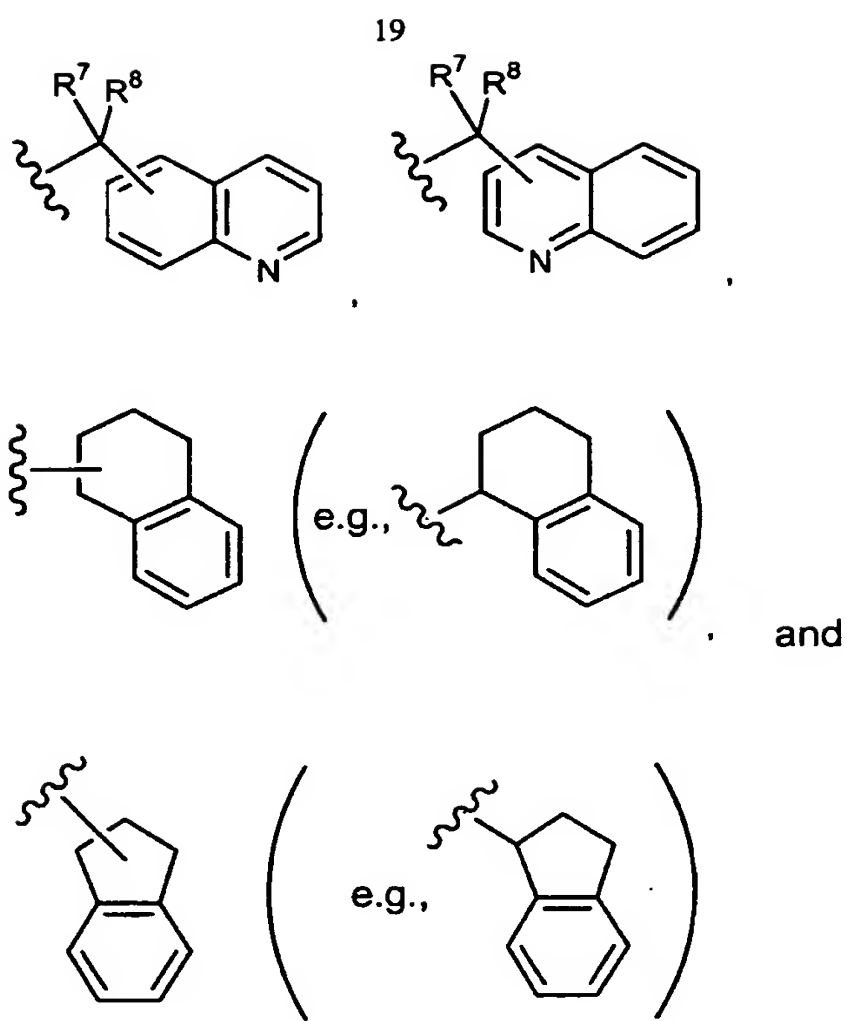
wherein the above rings of said A groups are substituted with 1 to 6 substituents each independently selected from the group consisting of: R⁹ groups;

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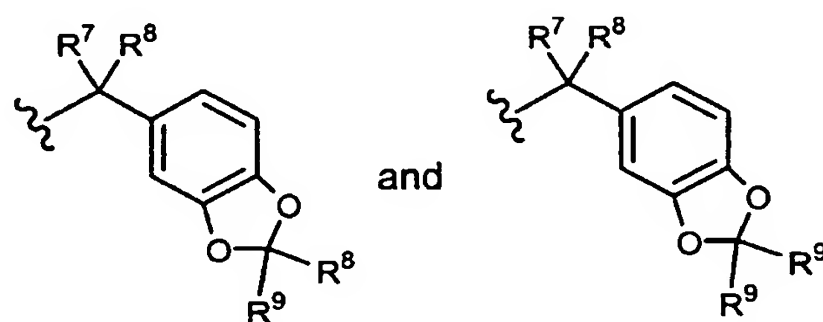


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wherein one or both of the above rings of said A groups are substituted with 1 to 6 substituents each independently selected from the group consisting of: R^9 groups;

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(4)

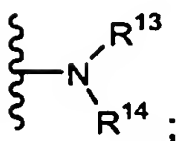
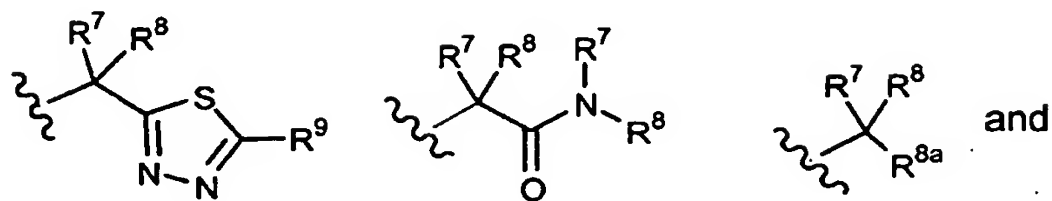
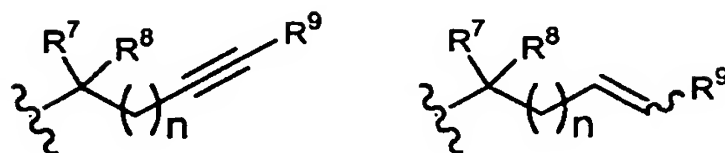
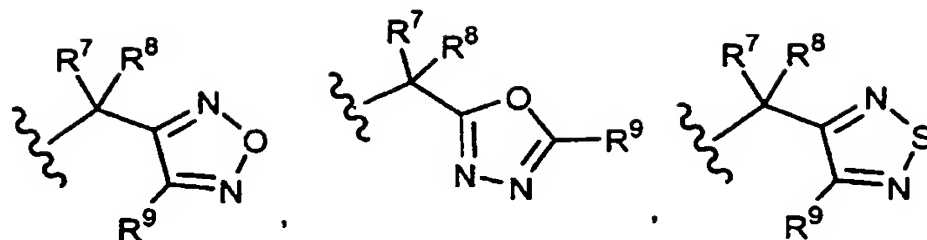


wherein the above phenyl rings of said A groups are substituted with 1 to 3 substituents each independently selected from the group consisting of: R^9 groups; and

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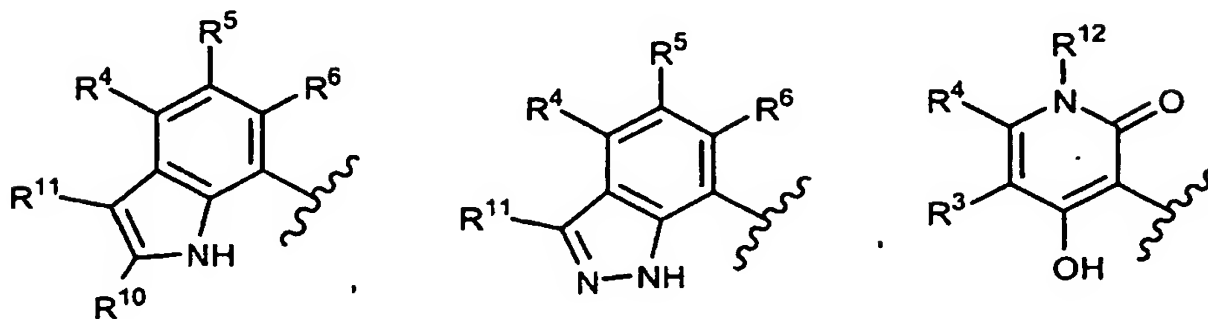
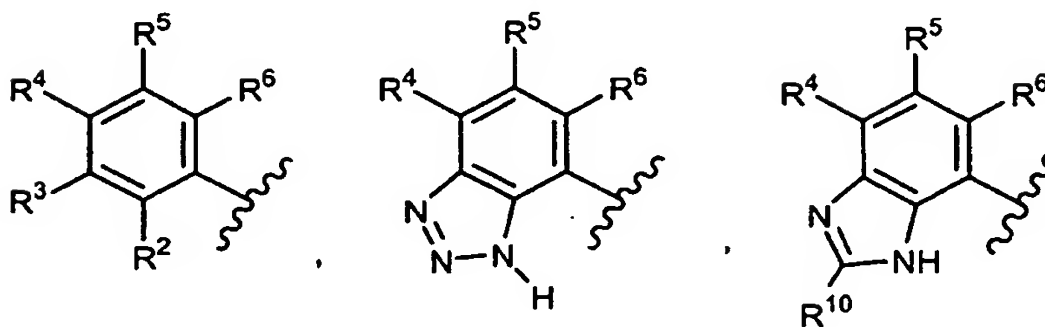
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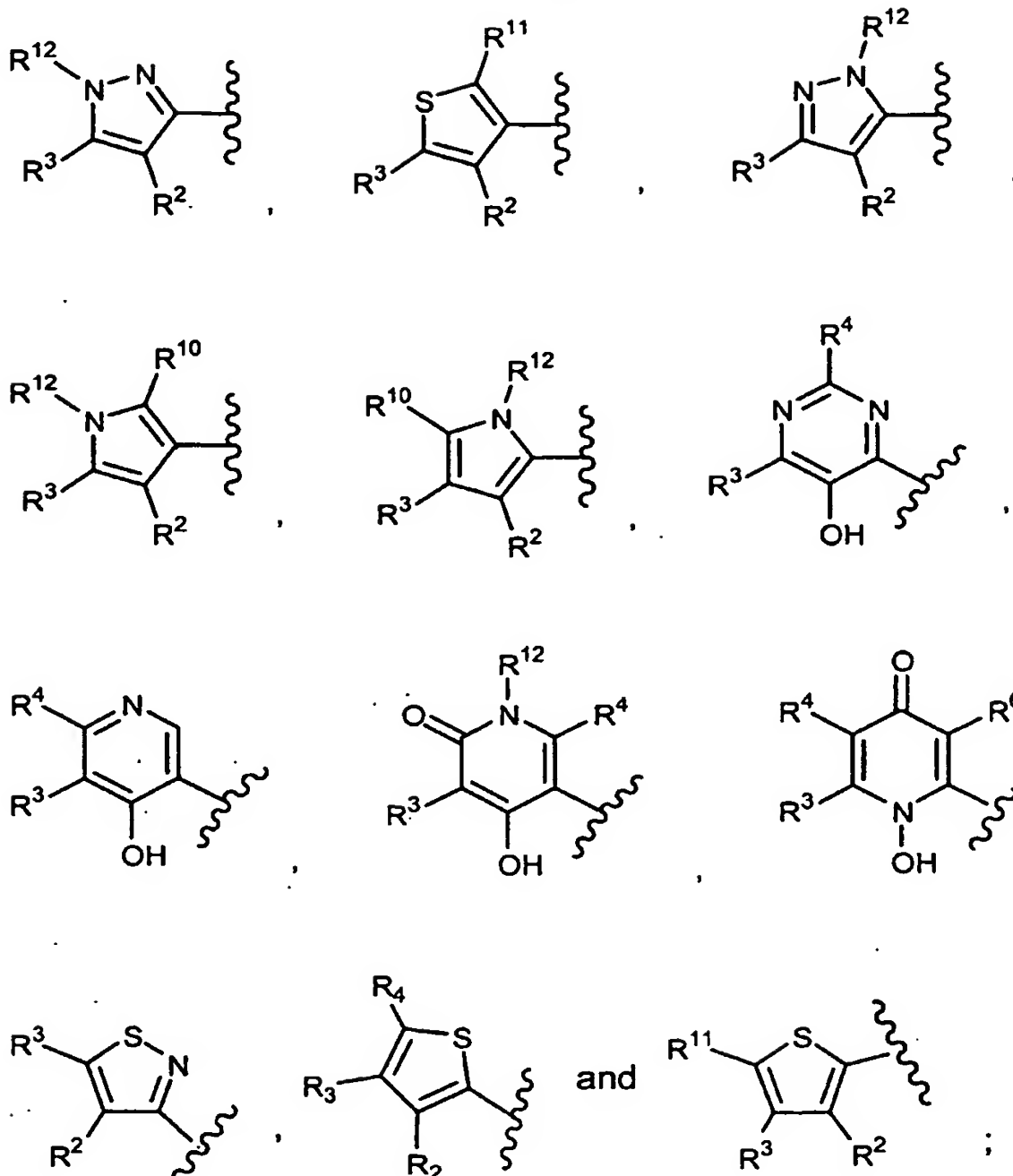
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B is selected from the group consisting of



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n is 0 to 6;

p is 1 to 5;

X is O, NH, or S;

Z is 1 to 3;

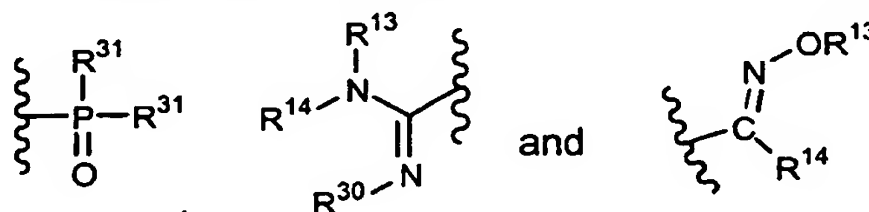
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R^2 is selected from the group consisting of: hydrogen, OH, $-C(O)OH$, $-SH$, $-SO_2NR^{13}R^{14}$, $-NHC(O)R^{13}$, $-NH SO_2NR^{13}R^{14}$, $-NH SO_2R^{13}$, $-NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, $-C(O)NHO R^{13}$, $-C(O)NR^{13}OH$, $-S(O_2)OH$, $-OC(O)R^{13}$, an unsubstituted heterocyclic acidic functional group, and a substituted heterocyclic acidic functional group; wherein there are 1 to 6 substituents on said substituted heterocyclic acidic functional group each substituent being independently selected from the group consisting of: R^9 groups;

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22

each R^3 and R^4 is independently selected from the group consisting of:
 hydrogen, cyano, halogen, alkyl, alkoxy, -OH, -CF₃, -OCF₃, -NO₂, -C(O)R¹³,
 -C(O)OR¹³, -C(O)NHR¹⁷, -C(O)NR¹³R¹⁴, -SO_(t)NR¹³R¹⁴, -SO_(t)R¹³, -C(O)NR¹³OR¹⁴,
 unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl,



5

wherein there are 1 to 6 substituents on said substituted aryl group and each
 substituent is independently selected from the group consisting of: R⁹ groups; and
 wherein there are 1 to 6 substituents on said substituted heteroaryl group and each
 substituent is independently selected from the group consisting of: R⁹ groups;

10

each R^5 and R^6 are the same or different and are independently selected
 from the group consisting of hydrogen, halogen, alkyl, alkoxy, -CF₃, -OCF₃,
 -NO₂, -C(O)R¹³, -C(O)OR¹³, -C(O)NR¹³R¹⁴, -SO_(t)NR¹³R¹⁴, -C(O)NR¹³OR¹⁴, cyano,
 unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl group;
 wherein there are 1 to 6 substituents on said substituted aryl group and each
 substituent is independently selected from the group consisting of: R⁹ groups; and
 wherein there are 1 to 6 substituents on said substituted heteroaryl group and each
 substituent is independently selected from the group consisting of: R⁹ groups;

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each R^7 and R^8 is independently selected from the group consisting of: H,
 unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or
 substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or
 substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or
 substituted cycloalkylalkyl, -CO₂R¹³, -CONR¹³R¹⁴, alkynyl, alkenyl, and cycloalkenyl;
 and wherein there are one or more (e.g., 1 to 6) substituents on said substituted R⁷
 and R⁸ groups, wherein each substituent is independently selected from the group
 consisting of:

25

- a) halogen,
- b) -CF₃,
- c) -COR¹³,
- d) -OR¹³,
- e) -NR¹³R¹⁴,
- f) -NO₂,

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- 5
- g) $-\text{CN}$,
 - h) $-\text{SO}_2\text{OR}^{13}$,
 - i) $-\text{Si}(\text{alkyl})_3$, wherein each alkyl is independently selected,
 - j) $-\text{Si}(\text{aryl})_3$, wherein each alkyl is independently selected,
 - 10 k) $-(\text{R}^{13})_2\text{R}^{14}\text{Si}$, wherein each R^{13} is independently selected,
 - l) $-\text{CO}_2\text{R}^{13}$,
 - m) $-\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$,
 - n) $-\text{SO}_2\text{NR}^{13}\text{R}^{14}$,
 - o) $-\text{SO}_2\text{R}^{13}$,
 - 10 p) $-\text{OC}(\text{O})\text{R}^{13}$,
 - q) $-\text{OC}(\text{O})\text{NR}^{13}\text{R}^{14}$,
 - r) $-\text{NR}^{13}\text{C}(\text{O})\text{R}^{14}$, and
 - s) $-\text{NR}^{13}\text{CO}_2\text{R}^{14}$;

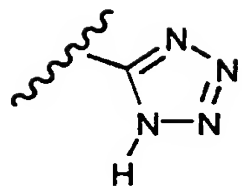
15 (fluoroalkyl is one non-limiting example of an alkyl group that is substituted with halogen);

R^{8a} is selected from the group consisting of: hydrogen, alkyl, cycloalkyl and cycloalkylalkyl;

each R^9 is independently selected from the group consisting of:

- 20
- a) $-\text{R}^{13}$,
 - b) halogen,
 - c) $-\text{CF}_3$,
 - d) $-\text{COR}^{13}$,
 - e) $-\text{OR}^{13}$,
 - f) $-\text{NR}^{13}\text{R}^{14}$,
 - 25 g) $-\text{NO}_2$,
 - h) $-\text{CN}$,
 - i) $-\text{SO}_2\text{R}^{13}$,
 - j) $-\text{SO}_2\text{NR}^{13}\text{R}^{14}$,
 - k) $-\text{NR}^{13}\text{COR}^{14}$,
 - 30 l) $-\text{CONR}^{13}\text{R}^{14}$,
 - m) $-\text{NR}^{13}\text{CO}_2\text{R}^{14}$,
 - n) $-\text{CO}_2\text{R}^{13}$,

o)



p) alkyl substituted with one or more (e.g., one) $-OH$ groups (e.g., $-(CH_2)_qOH$, wherein q is 1-6, usually 1 to 2, and preferably 1),

5 q) alkyl substituted with one or more (e.g., one) $-NR^{13}R^{14}$ group (e.g., $-(CH_2)_qNR^{13}R^{14}$, wherein q is 1-6, usually 1 to 2, and preferably 1), and

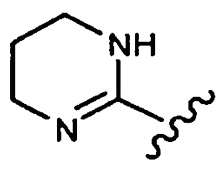
r) $-N(R^{13})SO_2R^{14}$ (e.g., R^{13} is H and R^{14} is alkyl, such as methyl);
each R^{10} and R^{11} is independently selected from the group consisting of R^{13} ,
(e.g., hydrogen and alkyl (e.g., C_1 to C_6 alkyl, such as methyl)), halogen, $-CF_3$, $-$
10 OCF_3 , $-NR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, $-OH$, $-C(O)OR^{13}$, $-SH$, $-SO_2NR^{13}R^{14}$, $-SO_2R^{13}$,
 $-NHC(O)R^{13}$, $-NHSO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, $-C(O)NR^{13}R^{14}$, $-C(O)NR^{13}OR^{14}$, $-$
 $OC(O)R^{13}$ and cyano;

R^{12} is selected from the group consisting of: hydrogen, $-C(O)OR^{13}$,
unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl,
15 unsubstituted or substituted arylalkyl, unsubstituted or substituted cycloalkyl,
unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkylalkyl, and
unsubstituted or substituted heteroarylalkyl group; wherein there are 1 to 6
substituents on the substituted R^{12} groups and each substituent is independently
selected from the group consisting of: R^9 groups;

20 each R^{13} and R^{14} is independently selected from the group consisting of: H,
unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or
substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or
substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or
substituted cycloalkylalkyl, unsubstituted or substituted heterocyclic, unsubstituted
25 or substituted fluoroalkyl, and unsubstituted or substituted heterocycloalkylalkyl
(wherein "heterocycloalkyl" means heterocyclic); wherein there are 1 to 6
substituents on said substituted R^{13} and R^{14} groups and each substituent is
independently selected from the group consisting of: alkyl, $-CF_3$, $-OH$, alkoxy, aryl,
arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, $-N(R^{40})_2$,
30 $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-S(O)_2NR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ provided that R^{15} is
not H, halogen, and $-NHC(O)NR^{15}R^{16}$; or

25

R^{13} and R^{14} taken together with the nitrogen they are attached to in the groups $-C(O)NR^{13}R^{14}$ and $-SO_2NR^{13}R^{14}$ form an unsubstituted or substituted saturated heterocyclic ring (preferably a 3 to 7 membered heterocyclic ring), said ring optionally containing one additional heteroatom selected from the group consisting of: O, S and NR^{18} ; wherein there are 1 to 3 substituents on the substituted cyclized R^{13} and R^{14} groups (i.e., there is 1 to 3 substituents on the ring formed when the R^{13} and R^{14} groups are taken together with the nitrogen to which they are bound) and each substituent is independently selected from the group consisting of: alkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-SO_2NR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ provided that R^{15} is not H, $-NHC(O)NR^{15}R^{16}$, $-NHC(O)OR^{15}$, halogen, and a heterocycloalkenyl group (i.e., a heterocyclic group that has at least one, and preferably one, double bond in a ring, e.g.,



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each R^{15} and R^{16} is independently selected from the group consisting of: H, alkyl, aryl, arylalkyl, cycloalkyl and heteroaryl;

R^{17} is selected from the group consisting of: $-SO_2$ alkyl, $-SO_2$ aryl, $-SO_2$ cycloalkyl, and $-SO_2$ heteroaryl;

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R^{18} is selected from the group consisting of: H, alkyl, aryl, heteroaryl, $-C(O)R^{19}$, $-SO_2R^{19}$ and $-C(O)NR^{19}R^{20}$;

each R^{19} and R^{20} is independently selected from the group consisting of: alkyl, aryl and heteroaryl;

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R^{30} is selected from the group consisting of: alkyl, cycloalkyl, $-CN$, $-NO_2$, or $-SO_2R^{15}$ provided that R^{15} is not H;

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each R^{31} is independently selected from the group consisting of: unsubstituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl and unsubstituted or substituted cycloalkyl; wherein there are 1 to 6 substituents on said substituted R^{31} groups and each substituent is independently selected from the group consisting of: alkyl, halogen and $-CF_3$;

each R^{40} is independently selected from the group consisting of: H, alkyl and cycloalkyl; and

t is 0, 1 or 2.

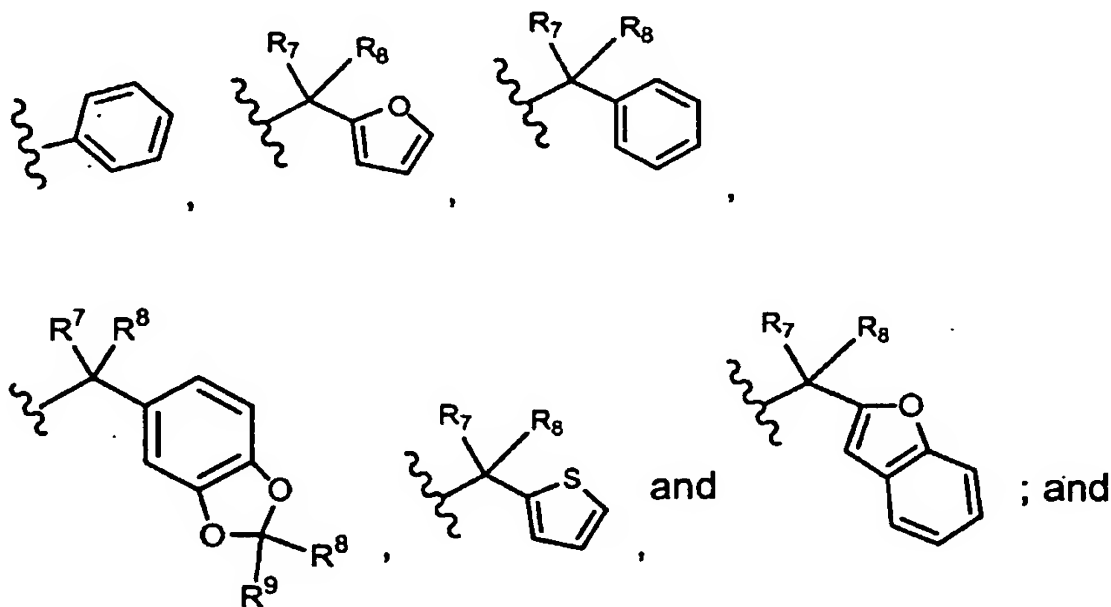
One embodiment of this invention is directed to the prodrugs of formula I and to the prodrugs of the pharmaceutically acceptable salts and solvates of formula I

In one embodiment of the this invention, when R³ in formula I is
5 -SO_(t)NR¹³R¹⁴ (e.g., -SO₂NR¹³R¹⁴), R¹³ and R¹⁴ are independently selected from the
group consisting of: H and alkyl (e.g., methyl, ethyl, isopropyl and t-butyl).
Examples include, but are not limited to (1) -SO₂NH₂ and (2) -SO₂NR¹³R¹⁴ wherein
R¹³ and R¹⁴ are the same or different alkyl group (e.g., methyl, ethyl, isopropyl and
t-butyl), e.g., the same alkyl group, such as, for example -SO₂N(CH₃)₂.

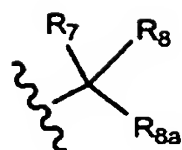
10 In another embodiment of this invention, when R³ in formula I is $-\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, R¹³ and R¹⁴ are independently selected from the group consisting of: H and alkyl (e.g., methyl, ethyl, isopropyl and t-butyl). Examples include, but are not limited to $-\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$ wherein each R¹³ and R¹⁴ are the same or different alkyl group, e.g., the same alkyl group, such as, for example $-\text{C}(\text{O})\text{N}(\text{CH}_3)_2$.

15 In another embodiment of this invention substituent A in formula I is selected from the group consisting of:

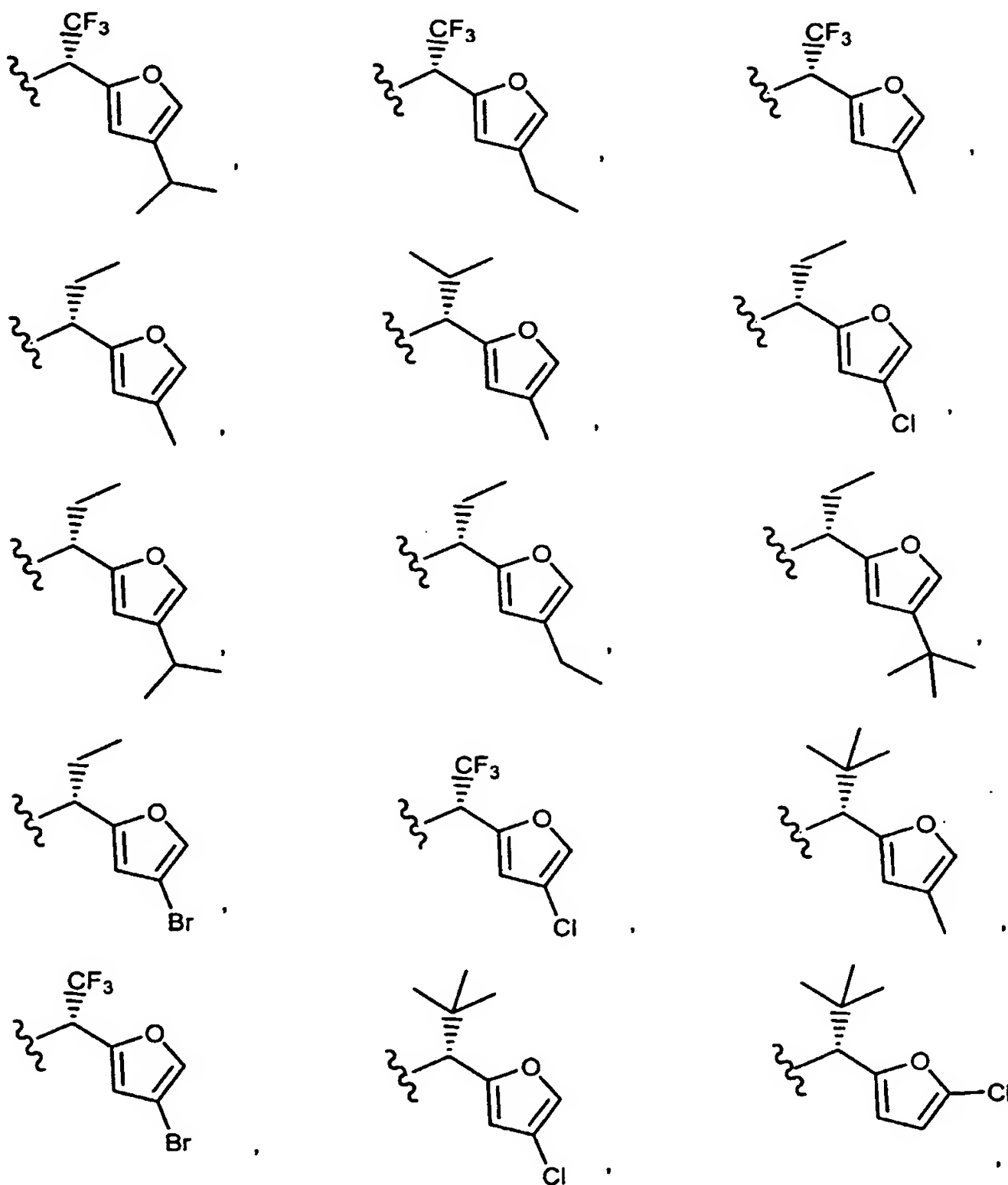
(1) unsubstituted or substituted:



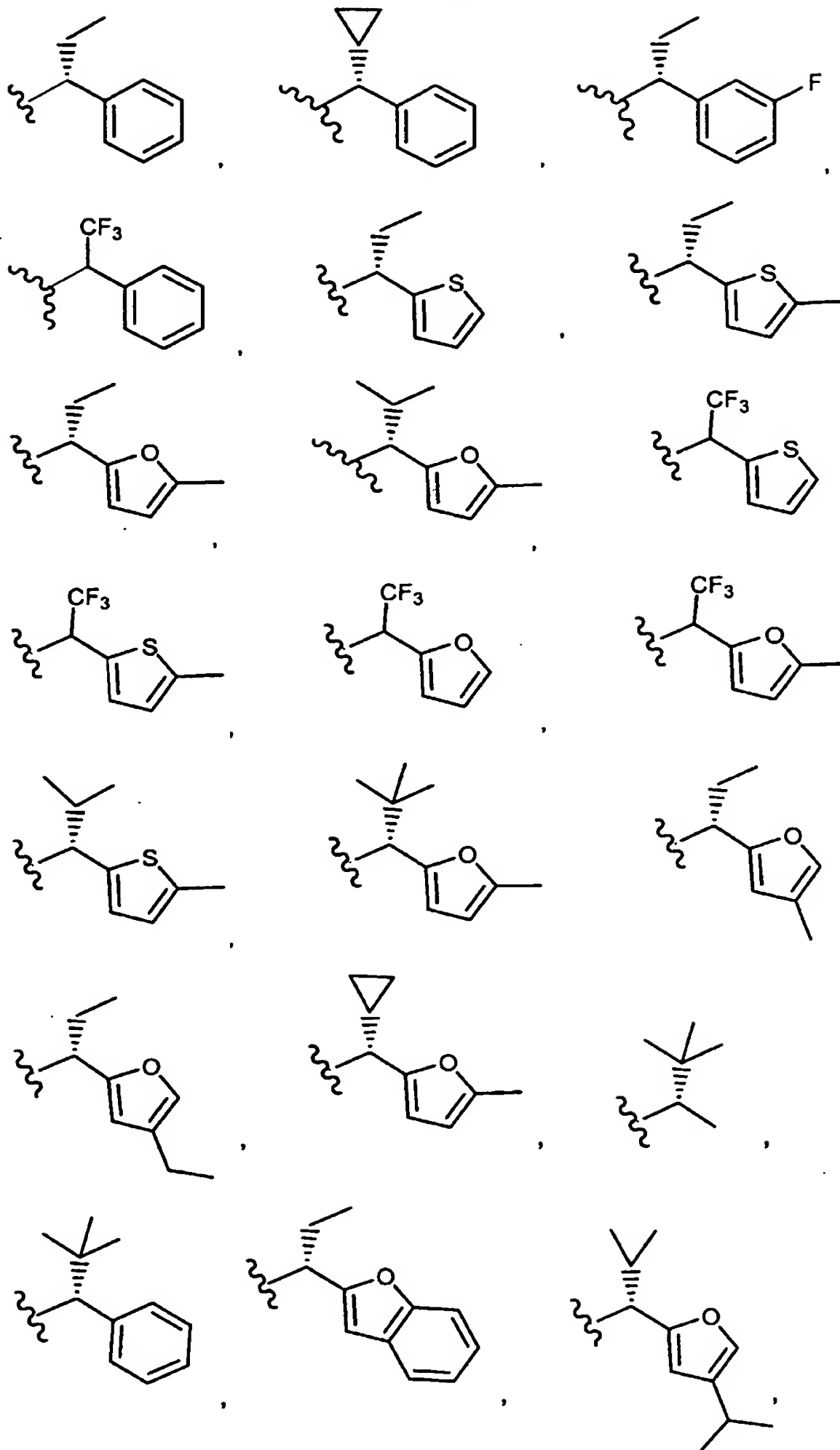
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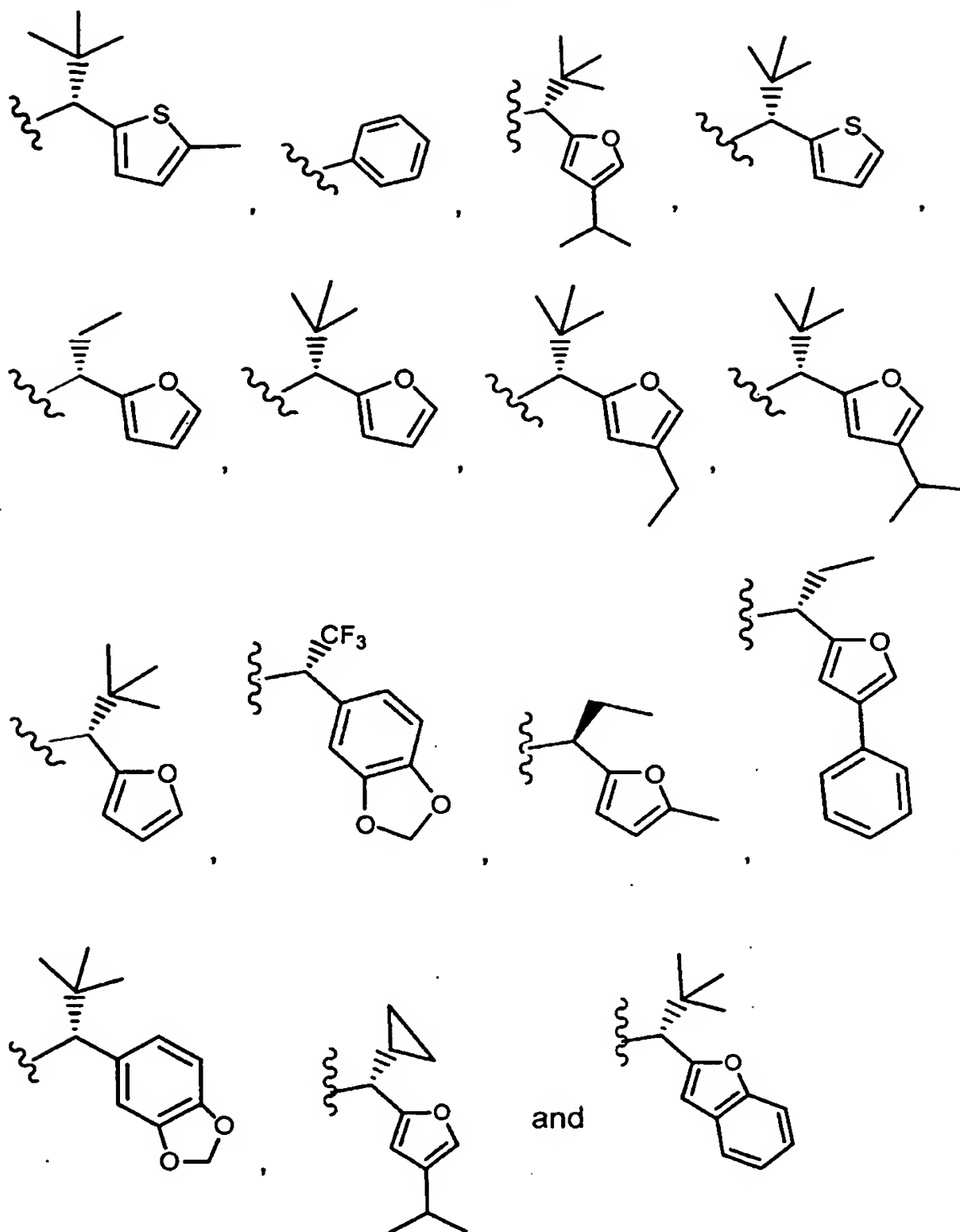
In another embodiment of this invention substituent A in formula I is selected
5 from the group consisting of:



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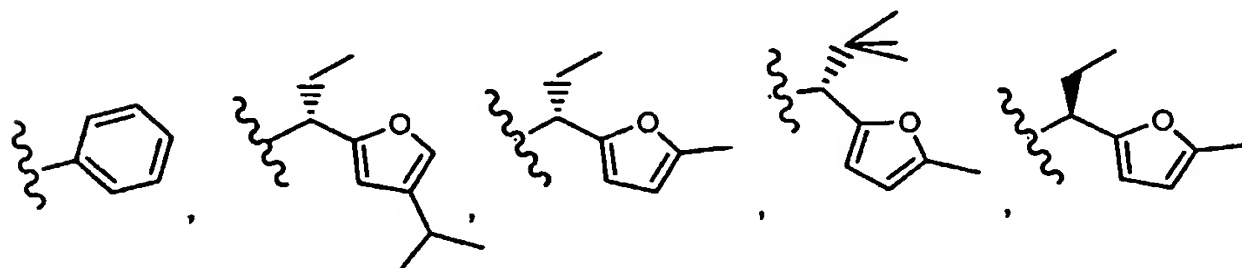


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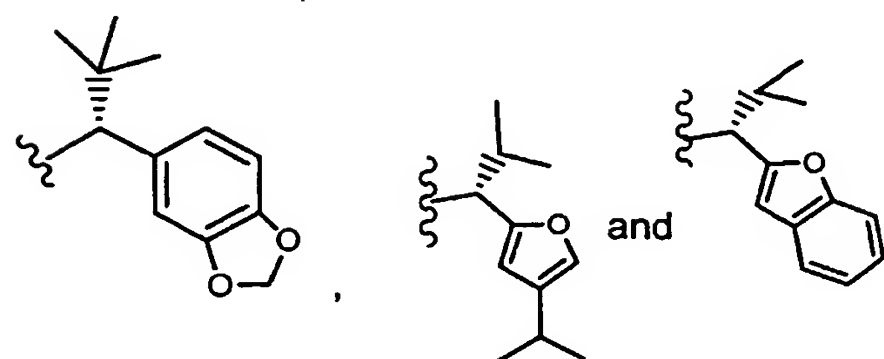
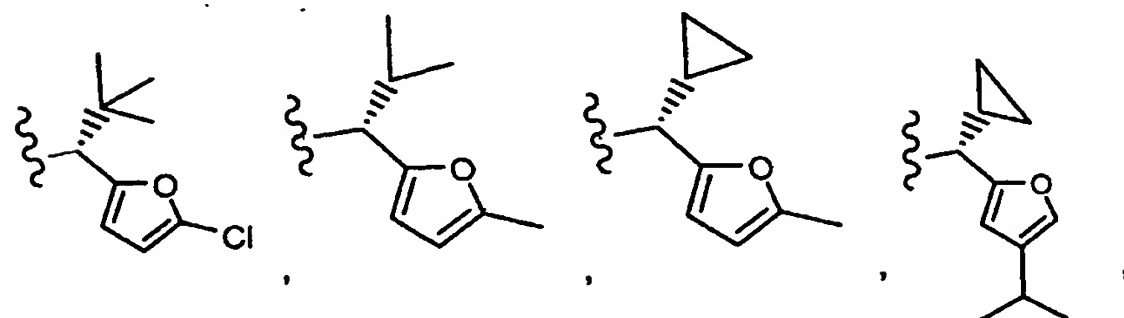
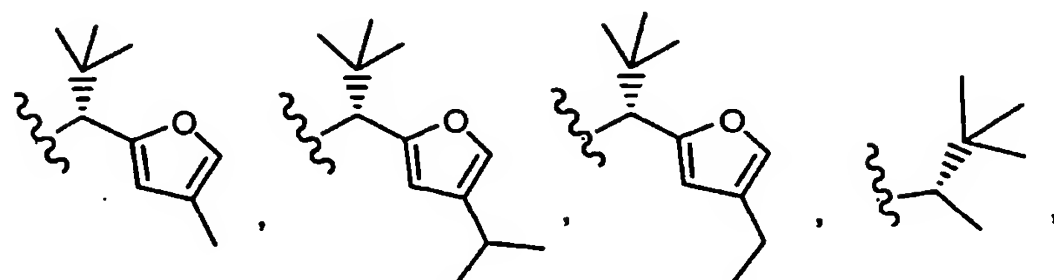
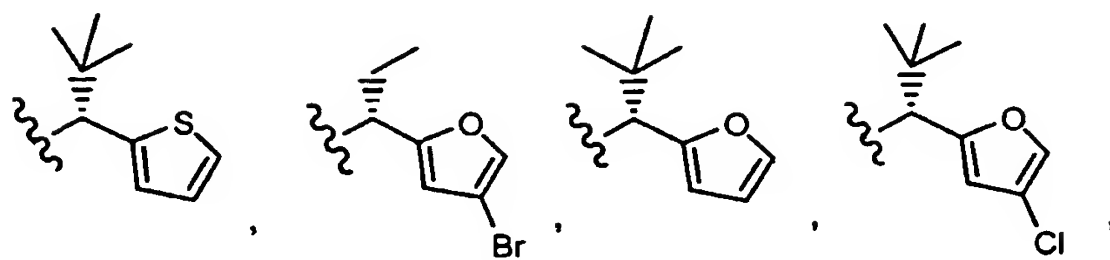
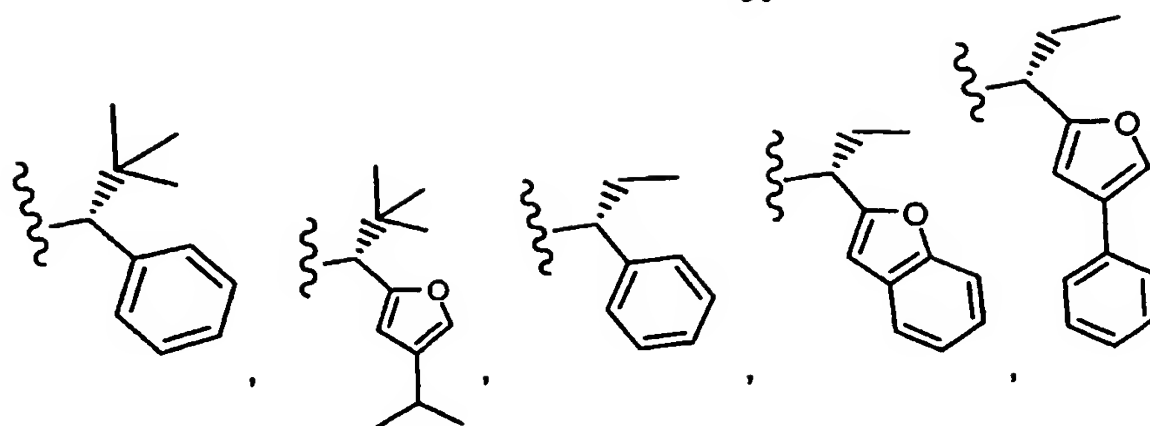


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In another embodiment of this invention substituent A in formula I is selected from the group consisting of:



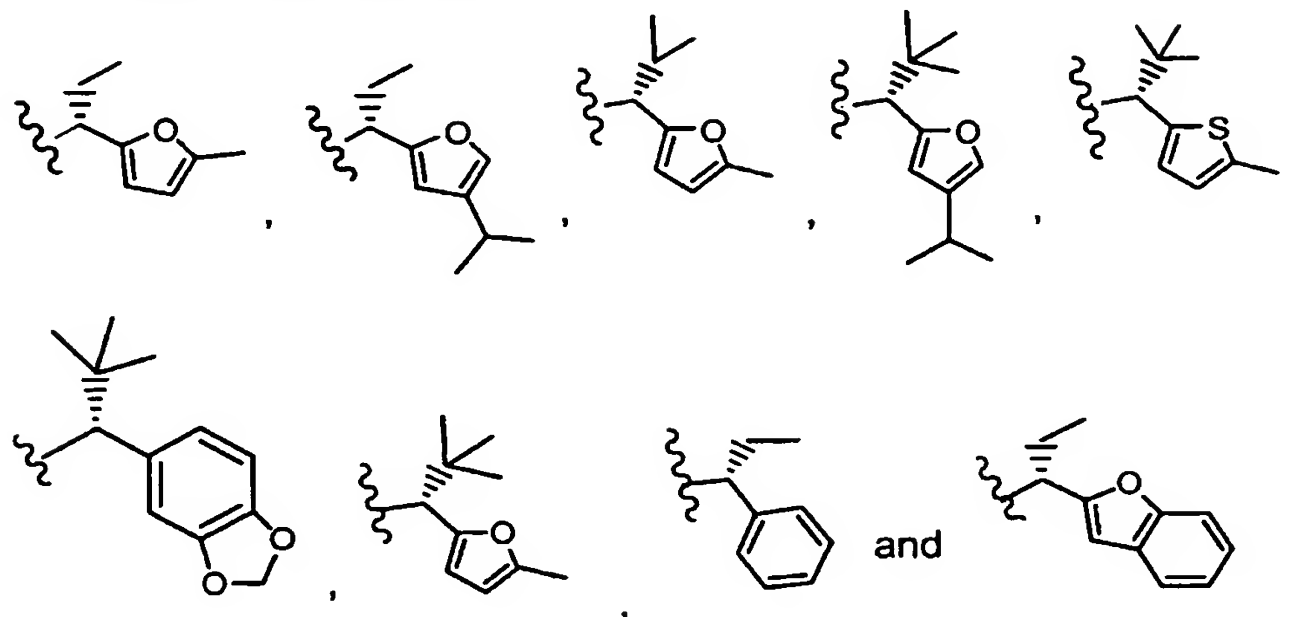
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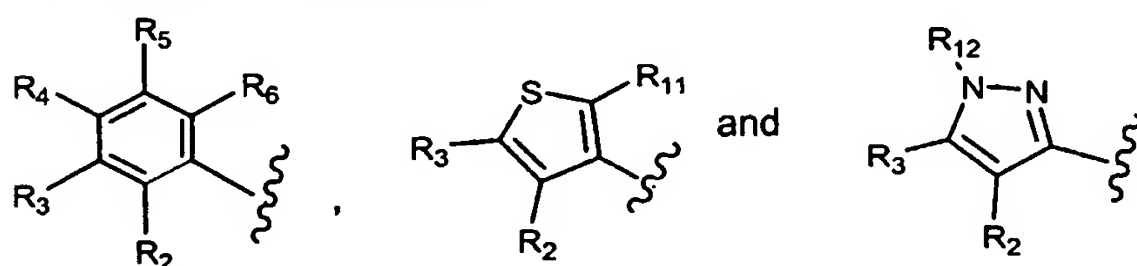
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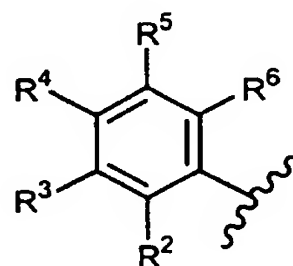
In another embodiment of this invention substituent A in formula I is selected from the group consisting of:



5 In another embodiment of this invention substituent B in formula I is selected from the group consisting of:

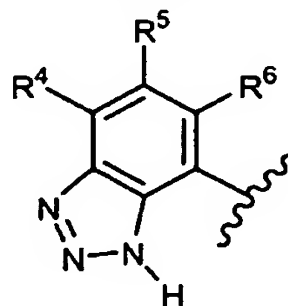


In another embodiment of this invention substituent B in formula I is:



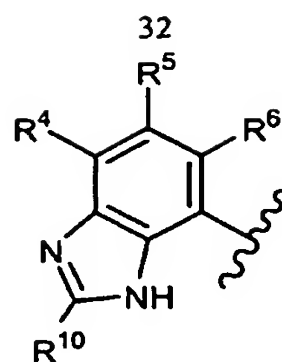
10 and all other substituents are as defined for of formula I.

In another embodiment of this invention substituent B in formula I is:



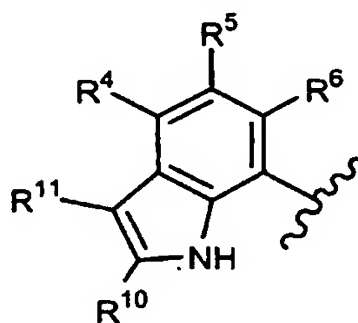
and all other substituents are as defined for of formula I.

In another embodiment of this invention substituent B in formula I is:



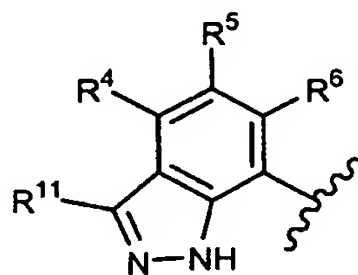
and all other substituents are as defined for of formula I.

In another embodiment of this invention substituent B in formula I is:



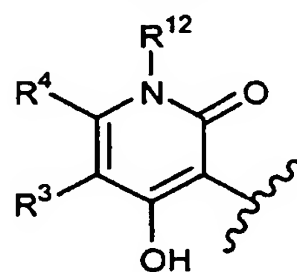
5 and all other substituents are as defined for of formula I.

In another embodiment of this invention substituent B in formula I is:



and all other substituents are as defined for of formula I.

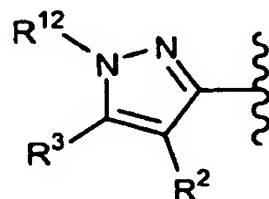
In another embodiment of this invention substituent B in formula I is:



10

and all other substituents are as defined for of formula I.

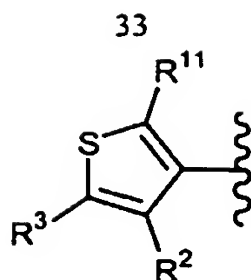
In another embodiment of this invention substituent B in formula I is:



and all other substituents are as defined for of formula I.

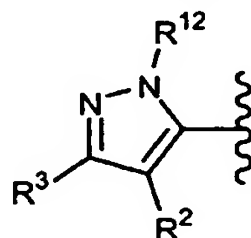
15

In another embodiment of this invention substituent B in formula I is:



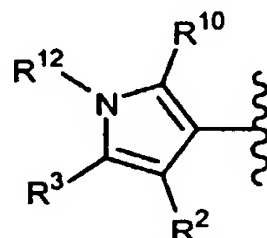
and all other substituents are as defined for of formula I.

In another embodiment of this invention substituent B in formula I is:



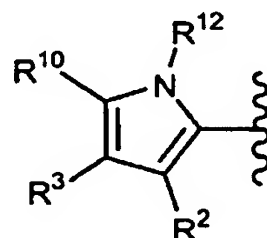
5 and all other substituents are as defined for of formula I.

In another embodiment of this invention substituent B in formula I is:



and all other substituents are as defined for of formula I.

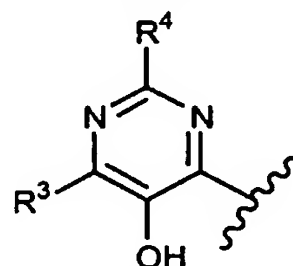
In another embodiment of this invention substituent B in formula I is:



10

and all other substituents are as defined for of formula I.

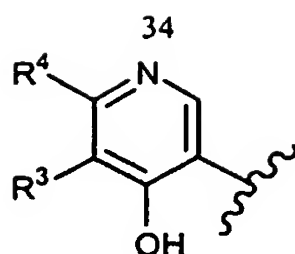
In another embodiment of this invention substituent B in formula I is:



and all other substituents are as defined for of formula I.

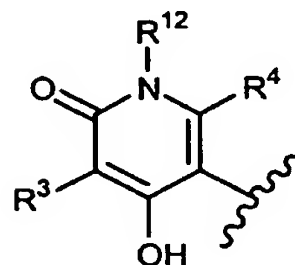
15

In another embodiment of this invention substituent B in formula I is:



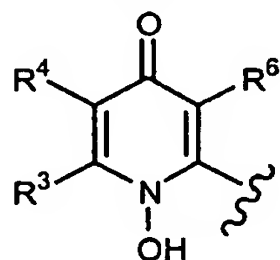
and all other substituents are as defined for of formula I.

In another embodiment of this invention substituent B in formula I is:



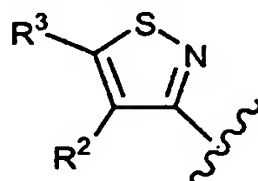
5 and all other substituents are as defined for of formula I.

In another embodiment of this invention substituent B in formula I is:



and all other substituents are as defined for of formula I.

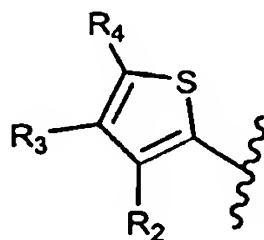
In another embodiment of this invention substituent B in formula I is:



10

and all other substituents are as defined for of formula I.

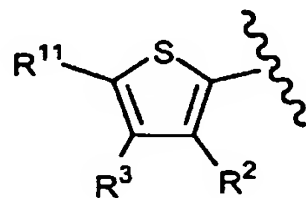
In another embodiment of this invention substituent B in formula I is:



and all other substituents are as defined for of formula I.

15

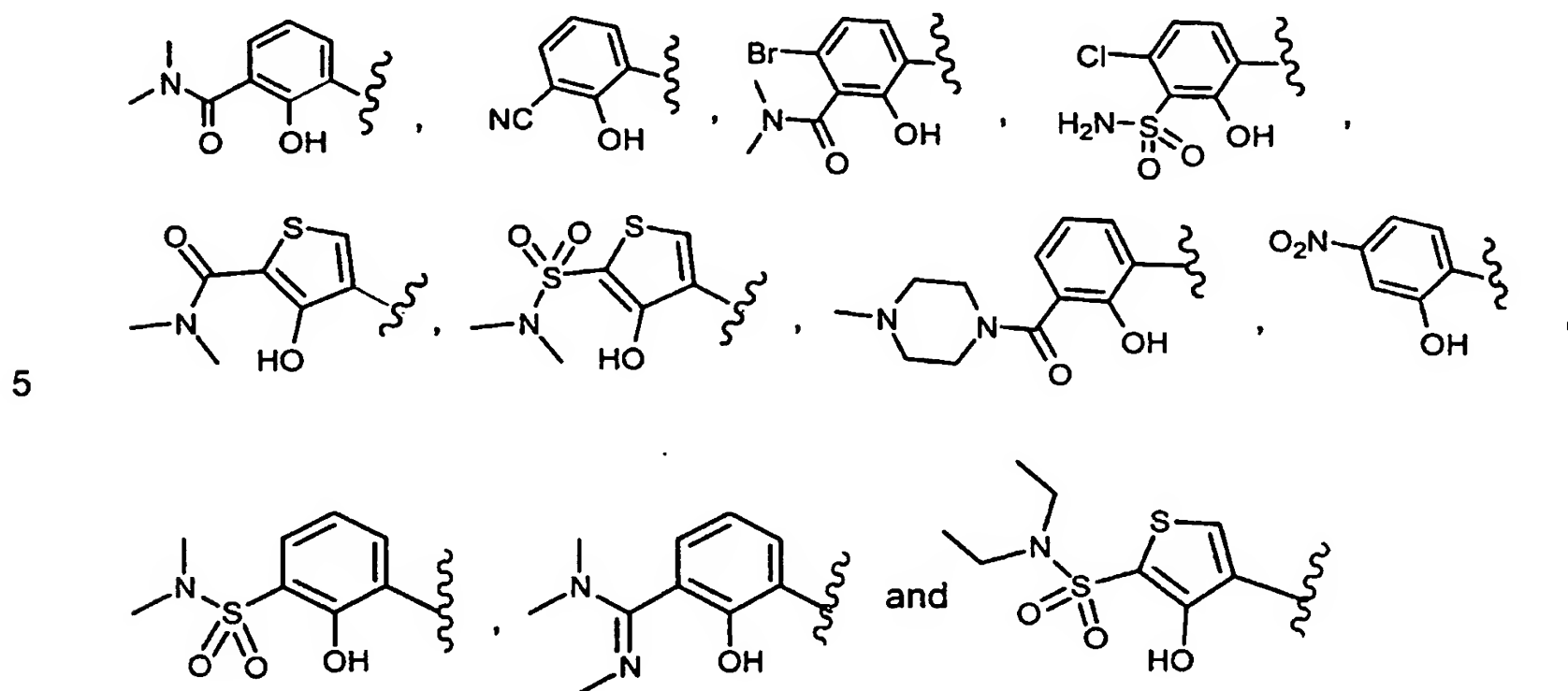
In another embodiment of this invention substituent B in formula I is:



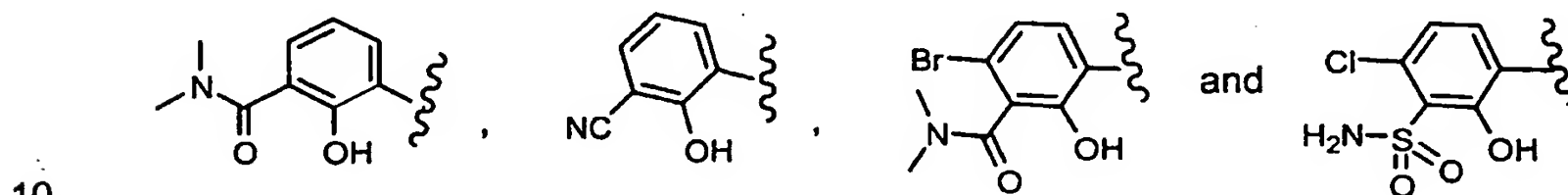
35

and all other substituents are as defined for of formula I.

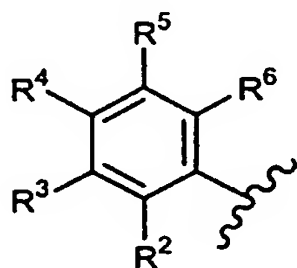
In another embodiment of this invention substituent B in formula I is selected from the group consisting of:



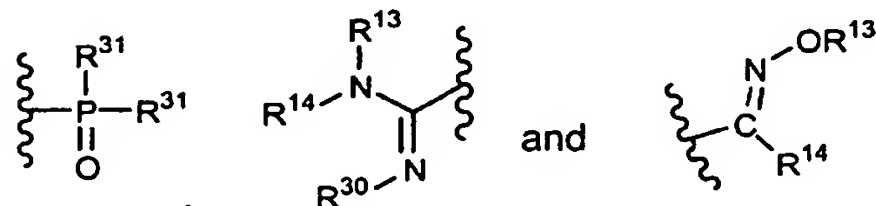
In another embodiment of this invention substituent B in formula I is selected from the group consisting of:



In another embodiment of this invention B is:

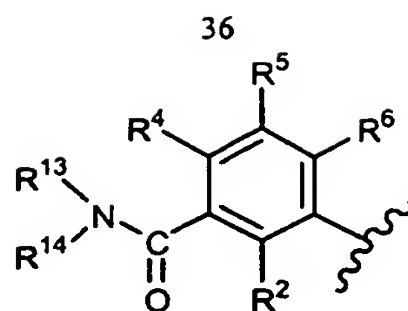


and R³ for this B group is selected from the group consisting of: -C(O)NR¹³R¹⁴,



and all other substituents are as defined for formula I.

In another embodiment of this invention substituent B in formula I is:



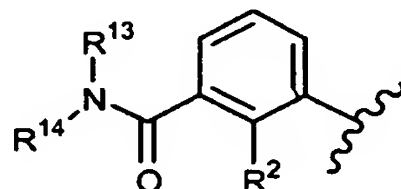
and all other substituents are as defined for formula I.

In another embodiment of this invention substituent B is:



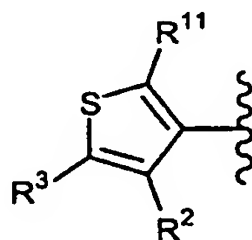
5 wherein R^2 is $-OH$, and all other substituents are as defined for formula I.

In another embodiment of this invention substituent B in formula I is:



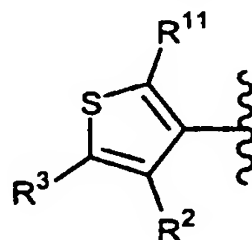
wherein R^2 is $-OH$, and R^{13} and R^{14} are independently selected from the group consisting of H and alkyl (e.g., methyl, ethyl, isopropyl and t-butyl).

10 In another embodiment of this invention substituent B in formula I is:



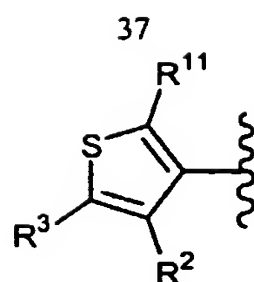
wherein R^{11} is H, and all other substituents are as defined for formula I.

In another embodiment of this invention substituent B in formula I is:



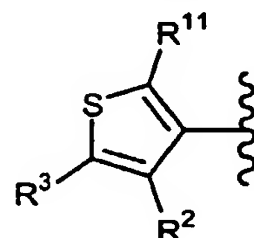
15 wherein R^2 is $-OH$, and all other substituents are as defined for formula I.

In another embodiment of this invention substituent B in formula I is:



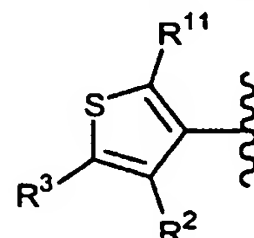
wherein R^3 is $-\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, and all other substituents are as defined for formula I.

In another embodiment of this invention substituent B in formula I is:



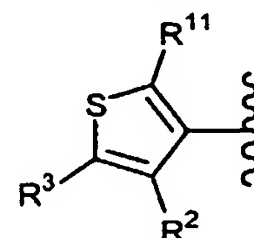
5 wherein R^3 is $-\text{S}(\text{O})_t\text{NR}^{13}\text{R}^{14}$, and all other substituents are as defined for formula I.

In another embodiment of this invention substituent B in formula I is:



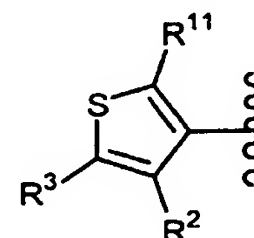
wherein R^2 is $-\text{OH}$, and R^3 is $-\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, and all other substituents are as defined for formula I.

10 In another embodiment of this invention substituent B in formula I is:



wherein R^2 is $-\text{OH}$, and R^3 is $-\text{S}(\text{O})_t\text{NR}^{13}\text{R}^{14}$, and all other substituents are as defined for formula I.

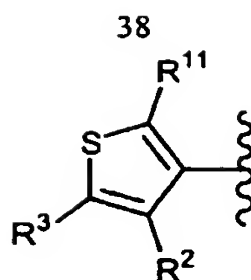
In another embodiment of this invention substituent B in formula I is:



15

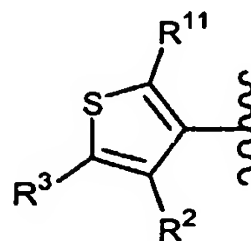
wherein R^2 is $-\text{OH}$, R^3 is $-\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, and R^{11} is H, and all other substituents are as defined for formula I.

In another embodiment of this invention substituent B in formula I is:



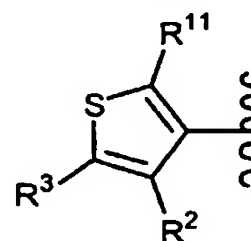
wherein R² is -OH, R³ is -S(O)_iNR¹³R¹⁴, and R¹¹ is H, and all other substituents are as defined for formula I.

In another embodiment of this invention substituent B in formula I is selected from the group consisting of:



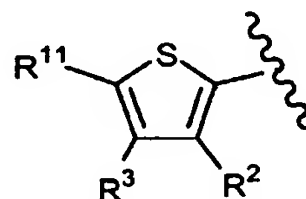
wherein R² is -OH, R³ is -C(O)NR¹³R¹⁴, R¹¹ is H, and R¹³ and R¹⁴ are independently selected from the group consisting of: H, alkyl (e.g., methyl, ethyl, isopropyl and t-butyl), unsubstituted heteroaryl and substituted heteroaryl.

In another embodiment of this invention substituent B in formula I is:



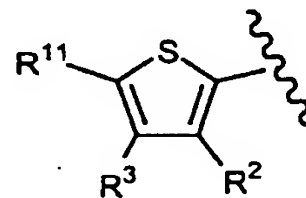
wherein R² is -OH, R³ is -S(O)_iNR¹³R¹⁴, R¹¹ is H, and R¹³ and R¹⁴ are independently selected from the group consisting of H and alkyl (e.g., methyl, ethyl, isopropyl and t-butyl).

In another embodiment of this invention substituent B in formula I is:



wherein R¹¹ is H, and all other substituents are as defined for formula I.

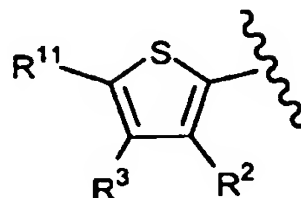
In another embodiment of this invention substituent B in formula I is:



wherein R² is -OH, and all other substituents are as defined for formula I.

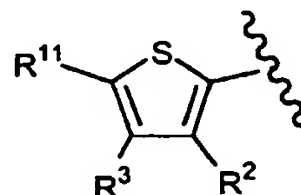
39

In another embodiment of this invention substituent B in formula I is:



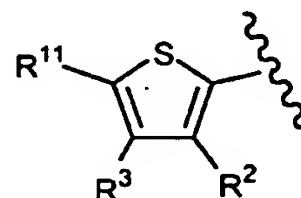
wherein R³ is $-\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, and all other substituents are as defined for formula I.

In another embodiment of this invention substituent B in formula I is:



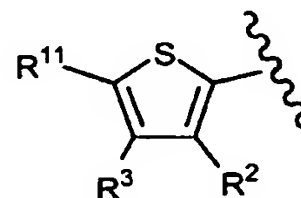
wherein R³ is $-\text{S}(\text{O})_t\text{NR}^{13}\text{R}^{14}$, and all other substituents are as defined for formula I.

In another embodiment of this invention substituent B in formula I is:



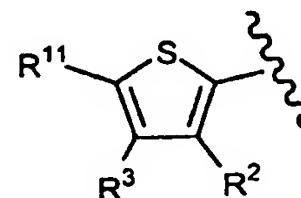
wherein R² is $-\text{OH}$, and R³ is $-\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, and all other substituents are as defined for formula I.

In another embodiment of this invention substituent B in formula I is:



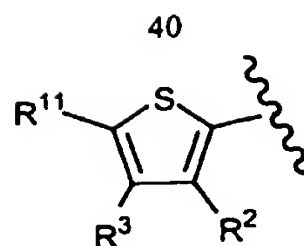
wherein R² is $-\text{OH}$, and R³ is $-\text{S}(\text{O})_t\text{NR}^{13}\text{R}^{14}$, and all other substituents are as defined for formula I.

In another embodiment of this invention substituent B in formula I is:



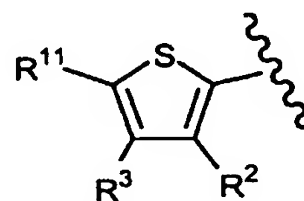
wherein R² is $-\text{OH}$, R³ is $-\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, and R¹¹ is H, and all other substituents are as defined for formula I.

In another embodiment of this invention substituent B in formula I is:



wherein R² is -OH, R³ is -S(O)_tNR¹³R¹⁴, and R¹¹ is H, and all other substituents are as defined for formula I.

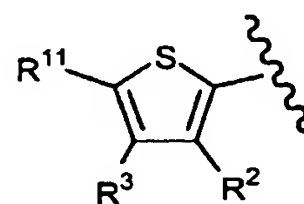
In another embodiment of this invention substituent B in formula I is:



5

wherein R² is -OH, R³ is -C(O)NR¹³R¹⁴, R¹¹ is H, and R¹³ and R¹⁴ are independently selected from the group consisting of: H, alkyl (e.g., methyl, ethyl, isopropyl and t-butyl), unsubstituted heteroaryl and substituted heteroaryl.

In another embodiment of this invention substituent B in formula I is:

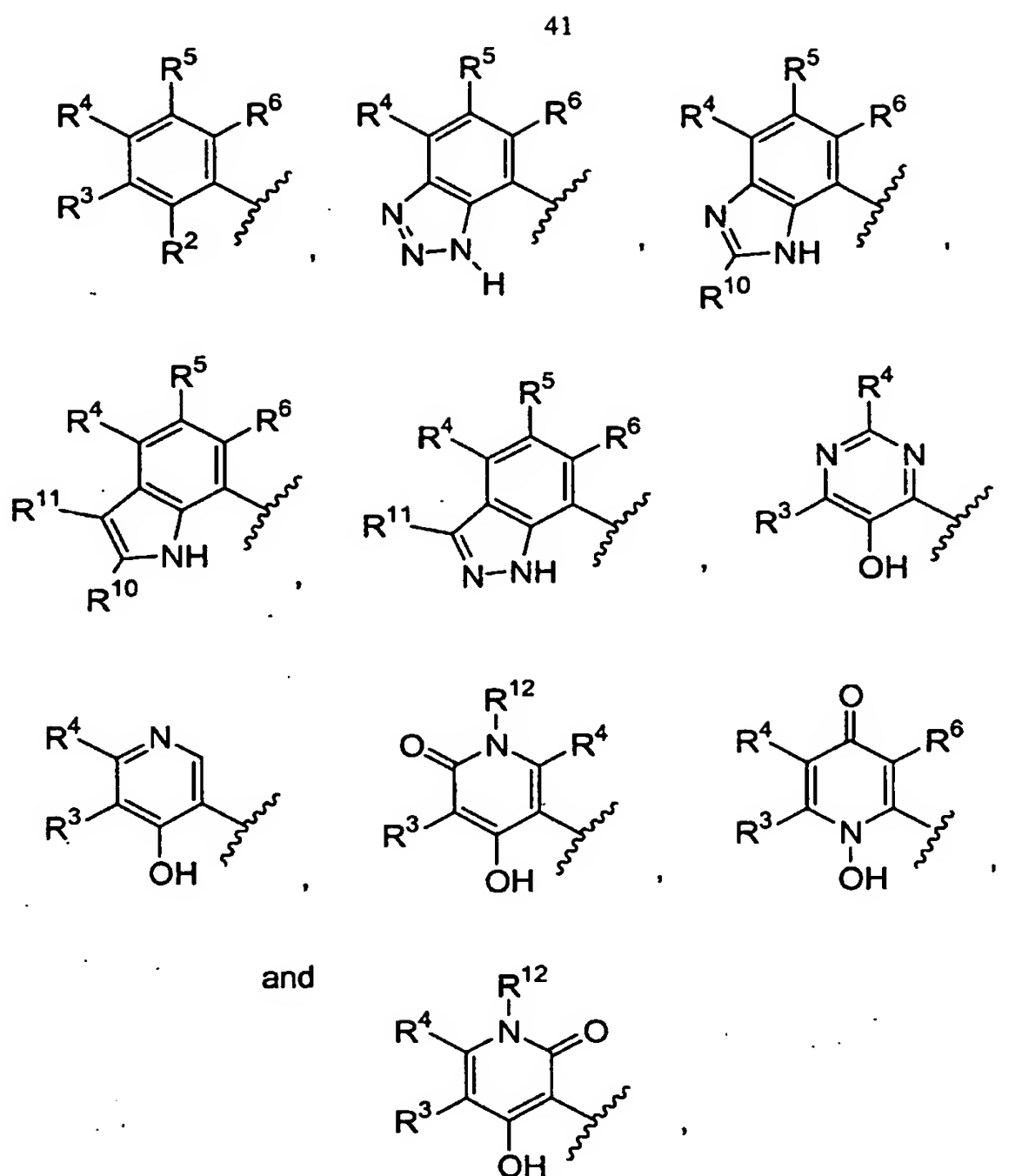


10

wherein R² is -OH, R³ is -S(O)_tNR¹³R¹⁴, R¹¹ is H, and R¹³ and R¹⁴ are independently selected from the group consisting of H and alkyl (e.g., methyl, ethyl, isopropyl and t-butyl).

In another embodiment of this invention substituent B is selected from the group consisting of:

15



wherein,

R^2 is hydrogen, OH, $C(O)OH$, SH, $SO_2NR^{13}R^{14}$, $NHC(O)R^{13}$, $NHSO_2NR^{13}R^{14}$, $NHSO_2R^{13}$, $NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)NHO R^{13}$, $C(O)NR^{13}OH$, $OC(O)R^{13}$ or an optionally substituted cyclic or heterocyclic acidic functional group, with the proviso that if R^2 is $SO_2NR^{13}R^{14}$, at least one of R^{13} and R^{14} must be hydrogen;

R^3 and R^4 are independently hydrogen, halogen, alkyl, alkoxy, OH, CF_3 , OCF_3 , NO_2 , $C(O)R^{13}$, $C(O)OR^{13}$, $C(O)NR^{13}R^{14}$, $SO_{(v)}NR^{13}R^{14}$, $SO_{(v)}R^{13}$,

$C(O)NR^{13}OR^{14}$, $C \equiv N-OR^{13}$, cyano, optionally substituted aryl or optionally substituted heteroaryl,

wherein the substituents on the optionally substituted groups may be selected from one or more R^9 groups.

R^5 and R^6 independently represent hydrogen, halogen, alkyl, alkoxy, CF_3 , OCF_3 , NO_2 , $C(O)R^{13}$, $C(O)OR^{13}$, $C(O)NR^{13}R^{14}$, $SO_{(t)}NR^{13}R^{14}$, $C(O)NR^{13}OR^{14}$,
 5 cyano, or an optionally substituted aryl or optionally substituted heteroaryl group,
 wherein the substituents on the optionally substituted groups may be selected from one or more R^9 groups.

R^{10} , R^{11} and R^{12} independently represent hydrogen, halogen, CF_3 , OCF_3 , $NR^{13}R^{14}$, $NR^{13}C(O)NR^{13}R^{14}$, OH , $C(O)OR^{13}$, SH , $SO_{(t)}NR^{13}R^{14}$, SO_2R^{13} , $NHC(O)R^{13}$,
 10 $NHSO_2NR^{13}R^{14}$, $NHSO_2R^{13}$, $C(O)NR^{13}R^{14}$, $C(O)NR^{13}OR^{14}$, $OC(O)R^{13}$, COR^{13} , OR^{13} , or cyano; and optionally substituted or unsubstituted: aryl, alkyl, arylalkyl, heteroaryl, aryloxy, heteroarylalkyl, heterocycloalkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxy and aminoalkyl;

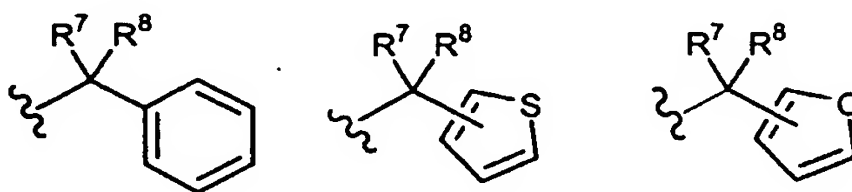
R^{13} and R^{14} are the same or different and are independently selected from
 15 the group consisting of H; and optionally substituted or unsubstituted: alkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, and fluoroalkyl; or R^{13} and R^{14} when taken together form an optionally substituted 3 to 7 membered heterocyclic ring containing one to two heteroatoms selected from O, S and N, and wherein, the substituents on the optionally substituted groups are selected from the
 20 group consisting of H, alkyl, aryl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, carbonyl and halogen.

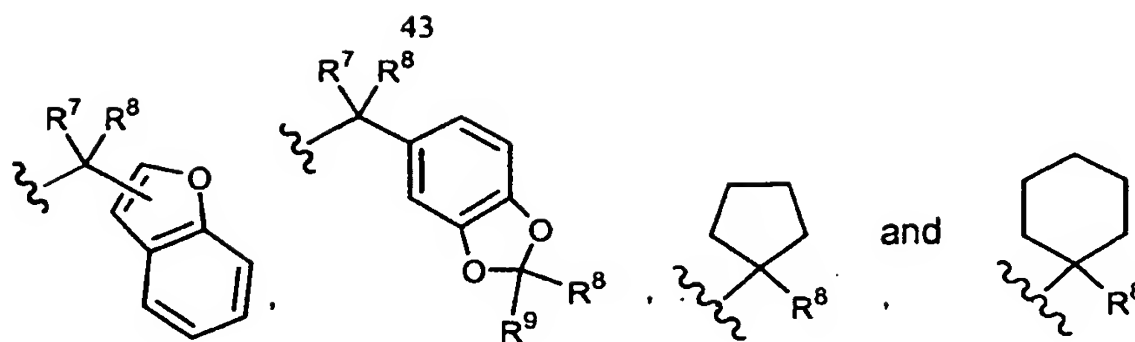
In another embodiment of this invention:

(1) substituent A in formula I is selected from the group consisting of:

25

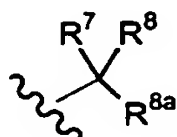
(a)





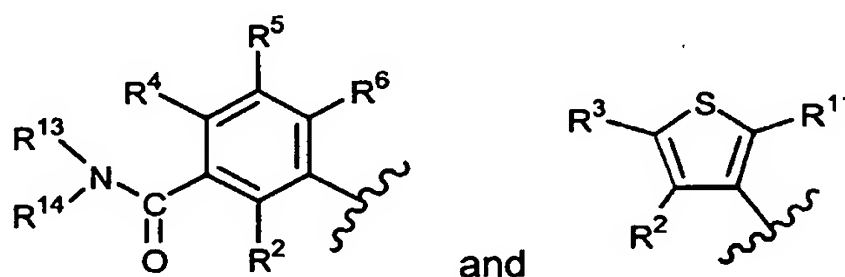
wherein the above rings are unsubstituted, or the above rings are substituted with 1 to 3 substituents independently selected from the group consisting of: H, F, Cl, Br, alkyl, cycloalkyl, and $-\text{CF}_3$; R^7 is selected from the group consisting of: H, $-\text{CF}_3$, $-\text{CF}_2\text{CH}_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and

(b)



wherein R^7 is selected from the group consisting of: H, $-\text{CF}_3$, $-\text{CF}_2\text{CH}_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and R^{8a} is as defined for formula I; and

(2) substituent B in formula I is selected from the group consisting of:



wherein:

R^2 is selected from the group consisting of: H, OH, $-\text{NHC}(\text{O})\text{R}^{13}$ and $-\text{NHSO}_2\text{R}^{13}$;

R^3 is selected from the group consisting of: $-\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, $-\text{SO}_2\text{NR}^{13}\text{R}^{14}$, $-\text{NO}_2$, cyano, $-\text{SO}_2\text{R}^{13}$; and $-\text{C}(\text{O})\text{OR}^{13}$;

R^4 is selected from the group consisting of: H, $-\text{NO}_2$, cyano, $-\text{CH}_3$ or $-\text{CF}_3$;

R^5 is selected from the group consisting of: H, $-\text{CF}_3$, $-\text{NO}_2$, halogen and cyano; and

R^6 is selected from the group consisting of: H, alkyl and $-\text{CF}_3$;

R^{11} is selected from the group consisting of: H, halogen and alkyl; and

each R^{13} and R^{14} is independently selected from the group consisting of: H, methyl, ethyl and isopropyl; or

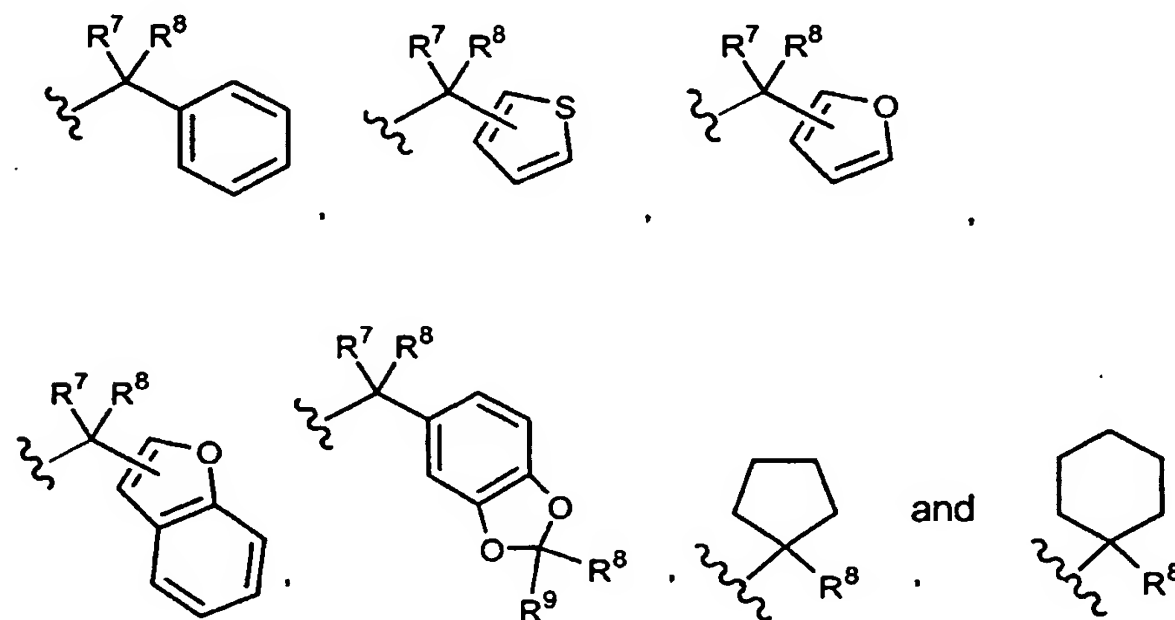
R^{13} and R^{14} when taken together with the nitrogen they are attached to in the groups $-NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, $-SO_2NR^{13}R^{14}$, $-OC(O)NR^{13}R^{14}$, $-CONR^{13}R^{14}$,
 5 $-NR^{13}C(O)NR^{13}R^{14}$, $-SO_2NR^{13}R^{14}$, $-NHCO_2NR^{13}R^{14}$ form an unsubstituted or substituted saturated heterocyclic ring (preferably a 3 to 7 membered ring) optionally having one additional heteroatom selected from O, S or NR¹⁸ wherein R^{18} is selected from H, alkyl, aryl, heteroaryl, $-C(O)R^{19}$, $-SO_2R^{19}$ and $-C(O)NR^{19}R^{20}$, wherein each R^{19} and R^{20} is independently selected from alkyl, aryl and heteroaryl,
 10 wherein there are 1 to 3 substituents on the substituted cyclized R^{13} and R^{14} groups and each substituent is independently selected from the group consisting of: alkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-SO_2NR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ provided that R^{15} is not H, $-NHC(O)NR^{15}R^{16}$ and
 15 halogen; and wherein each R^{15} and R^{16} is independently selected from the group consisting of: H, alkyl, aryl, arylalkyl, cycloalkyl and heteroaryl.

In another embodiment of this invention:

(1) substituent A in formula I is selected from the group consisting of:

20

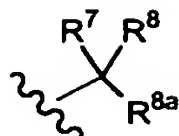
(a)



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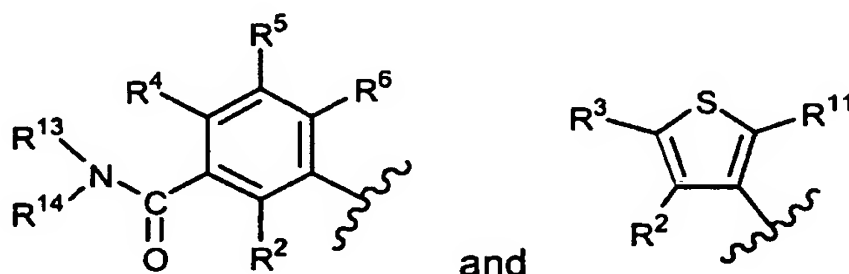
wherein the above rings are unsubstituted, or the above rings are substituted with 1 to 3 substituents independently selected from the group consisting of: F, Cl, Br, alkyl, cycloalkyl, and $-CF_3$; R^7 is selected from the group consisting of: H, $-CF_3$, $-CF_2CH_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and

(b)



wherein R^7 is selected from the group consisting of: H, $-CF_3$, $-CF_2CH_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and R^{8a} is as defined for formula I; and

(2) substituent B in formula I is selected from the group consisting of:



wherein:

R^2 is selected from the group consisting of: H, OH, $-NHC(O)R^{13}$ and $-NHSO_2R^{13}$;

R^3 is selected from the group consisting of: $-C(O)NR^{13}R^{14}$, $-SO_2NR^{13}R^{14}$, $-NO_2$, cyano, and $-SO_2R^{13}$;

R^4 is selected from the group consisting of: H, $-NO_2$, cyano, $-CH_3$ or $-CF_3$;

R^5 is selected from the group consisting of: H, $-CF_3$, $-NO_2$, halogen and cyano; and

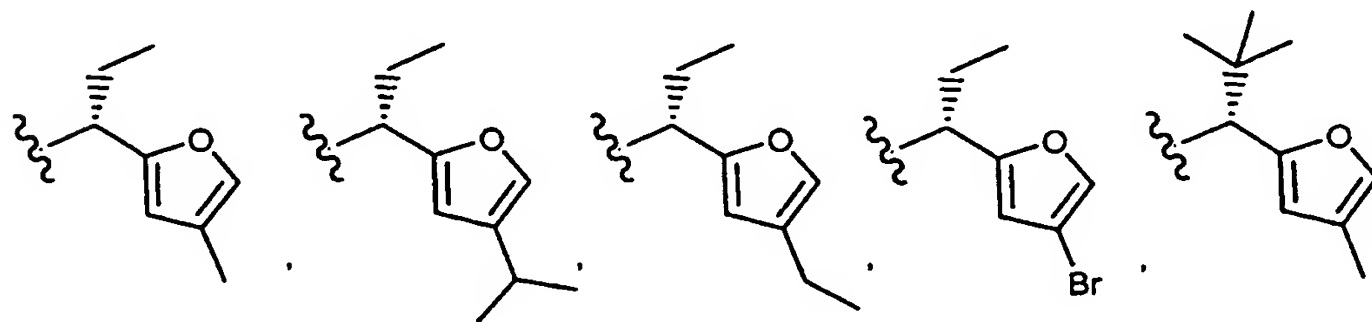
R^6 is selected from the group consisting of: H, alkyl and $-CF_3$;

R^{11} is selected from the group consisting of: H, halogen and alkyl; and

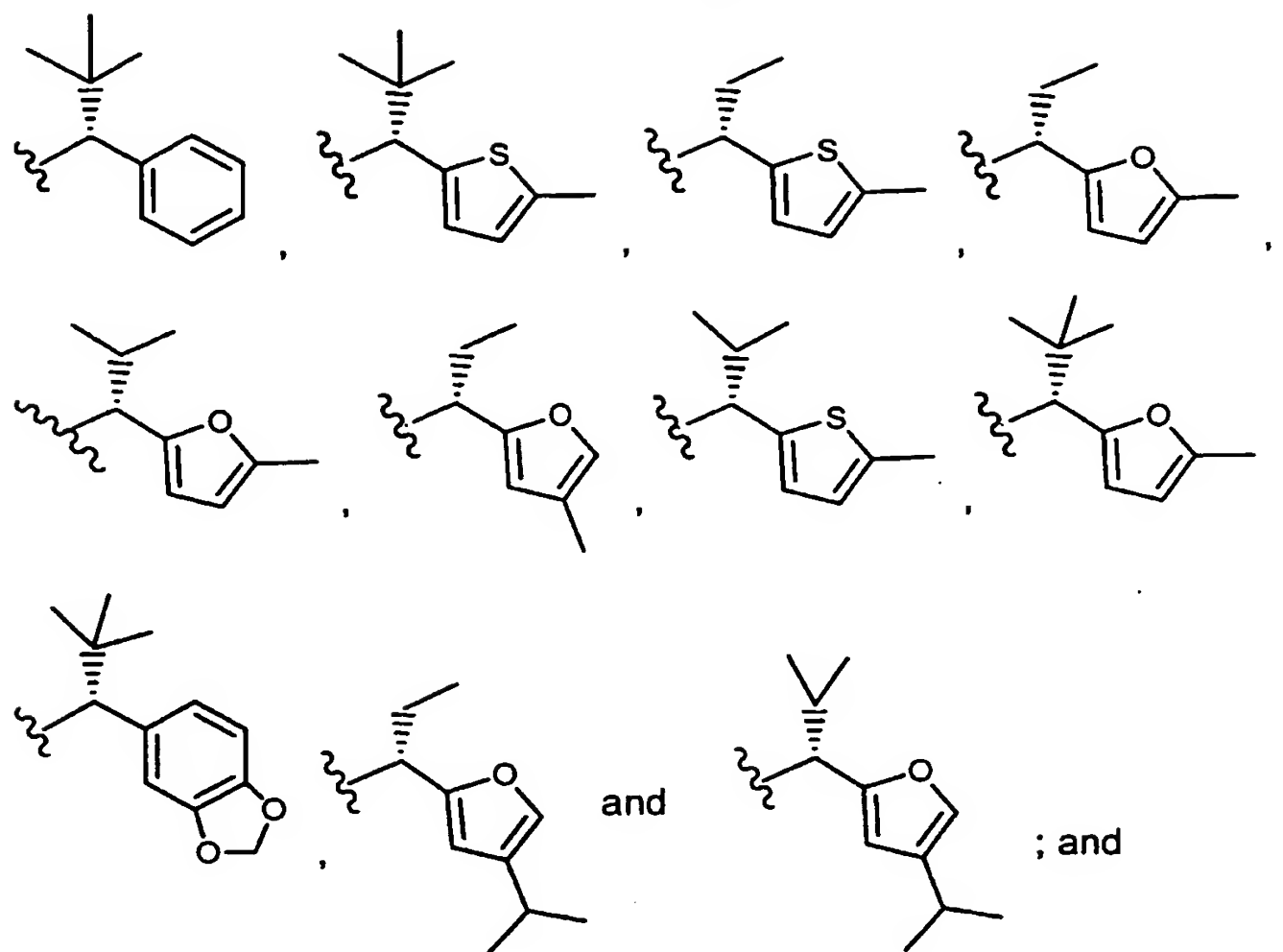
each R^{13} and R^{14} is independently selected from the group consisting of: H, methyl and ethyl.

In another embodiment of this invention:

(1) substituent A in formula I is selected from the group consisting of:



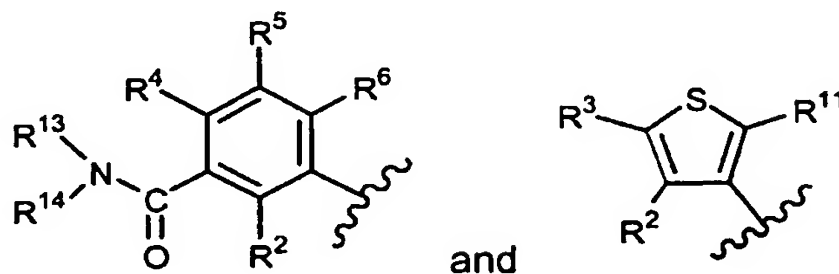
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(2) substituent B in formula I is selected from the group consisting

of:



and

wherein:

 R^2 is $-OH$;

10

 R^3 is selected from the group consisting of: $-SO_2NR^{13}R^{14}$ and $-CONR^{13}R^{14}$; R^4 is selected from the group consisting of: H, $-CH_3$ and $-CF_3$; R^5 is selected from the group consisting of: H and cyano; R^6 is selected from the group consisting of: H, $-CH_3$ and $-CF_3$; R^{11} is H; and

15

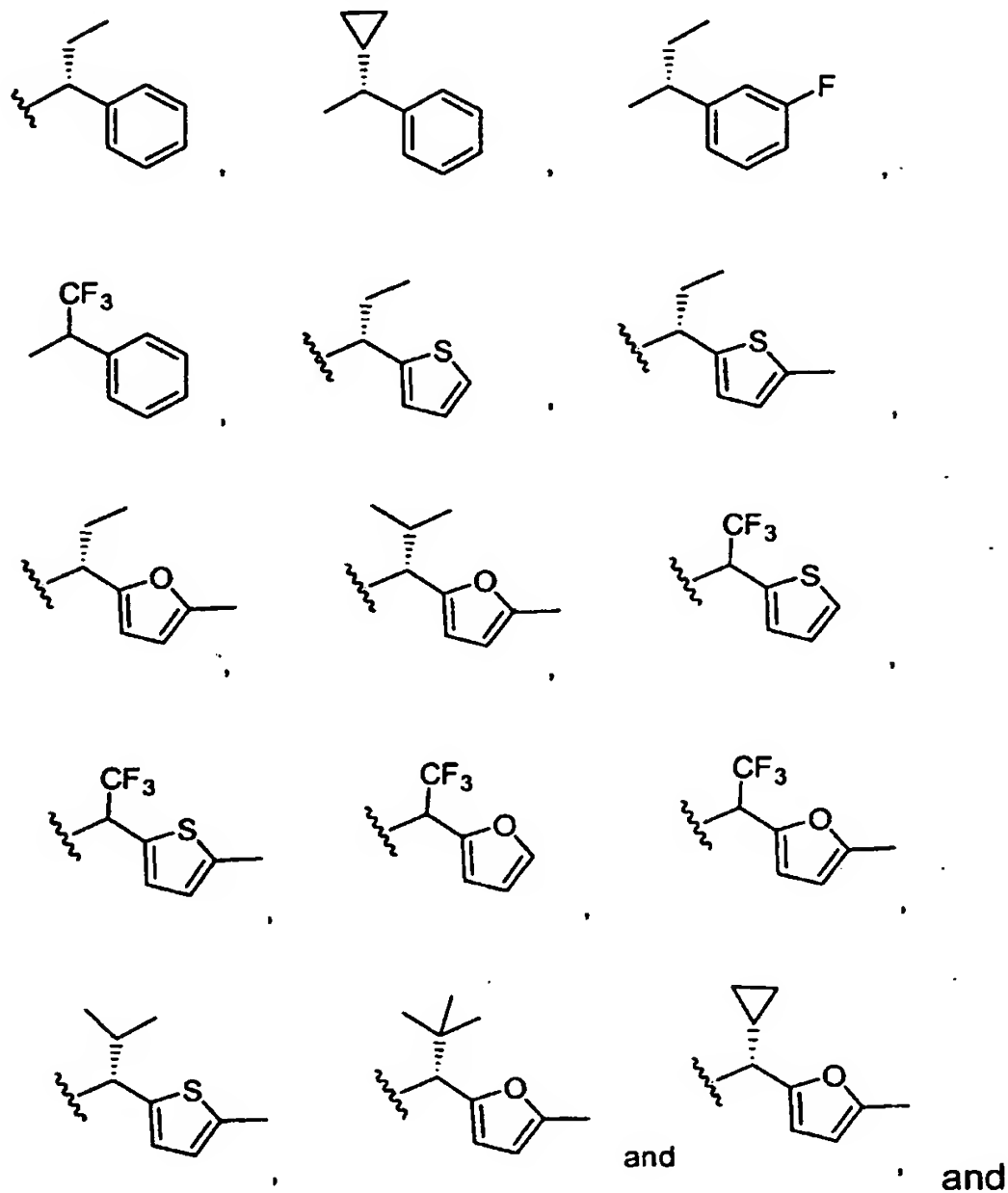
 R^{13} and R^{14} are independently selected from the group consisting of H and

methyl.

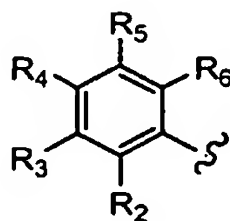
In another embodiment of this invention:

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(1) substituent A is selected from the group consisting of:



(2) substituent B is:



5.

wherein,

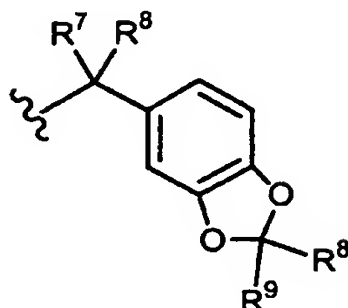
 R^2 is $-OH$; R^3 is $CONR^{13}R^{14}$; R^4 is selected from the group consisting of H, CF_3 and CH_3 ;

10

 R^5 is H and cyano; R^6 is selected from the group consisting of H, CH_3 and CF_3 ; R^{13} and R^{14} are methyl.

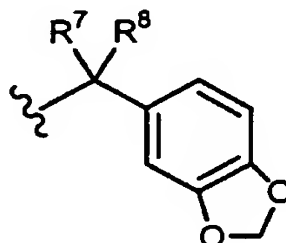
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In another embodiment of this invention, B is as described in any one of the above embodiments, and A is:



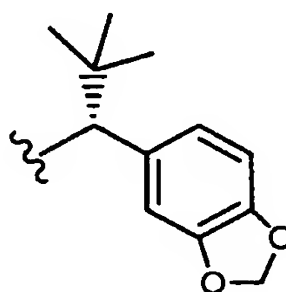
and all other substituents are as defined for formula I.

5 In another embodiment of this invention, B is as described in any one of the above embodiments, and A is:



wherein R^7 is H, and R^8 is alkyl (e.g., methyl, ethyl, isopropyl, cyclopropyl and t-butyl), and all other substituents are as defined for formula I.

10 In another embodiment of this invention, B is as described in any one of the above embodiments, and A is:



and all other substituents are as defined for formula I.

15 In another embodiment of this invention, R^1 in formula I is selected from the group consisting of: H, alkyl, aryl and cycloalkyl.

In another embodiment of this invention, R^1 in formula I is selected from the group consisting of: H, methyl, phenyl and cyclohexyl.

In another embodiment of this invention, R^1 in formula I is selected from the group consisting of: H, methyl, aryl and cyclohexyl.

20 In another embodiment of this invention, R^{15} in formula I is selected from the group consisting of: H, alkyl, aryl and cycloalkyl.

In another embodiment of this invention, R^{15} in formula I is selected from the group consisting of: H, methyl, phenyl and cyclohexyl.

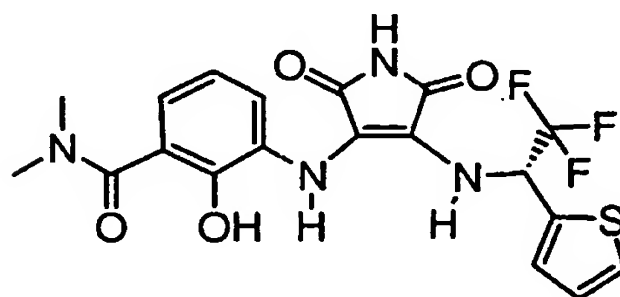
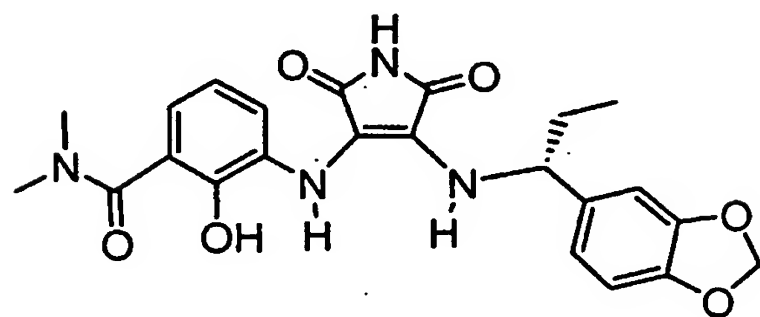
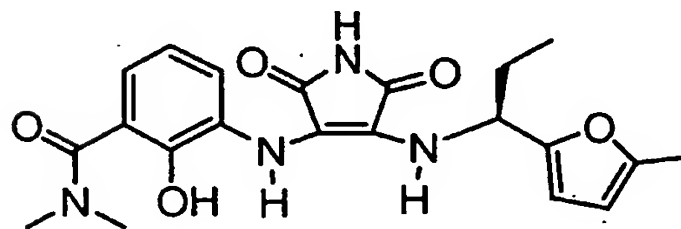
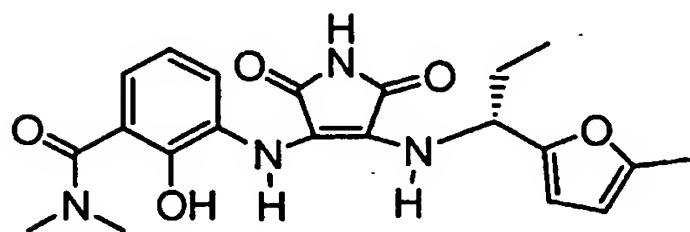
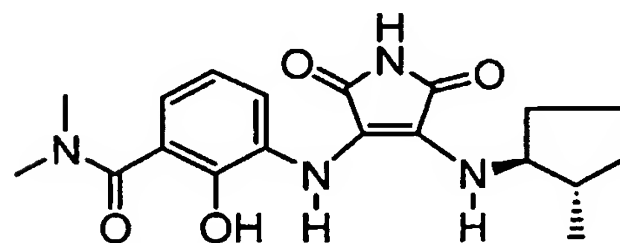
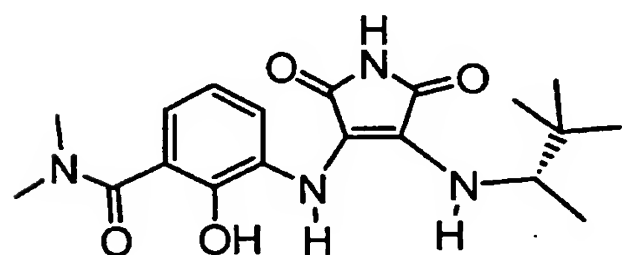
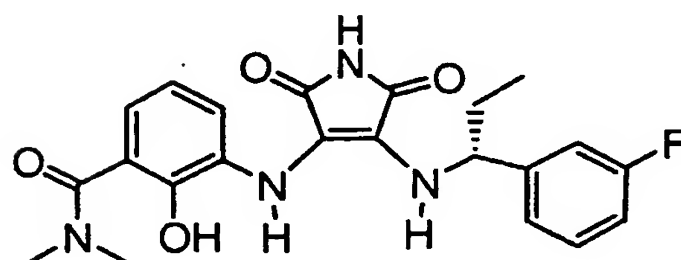
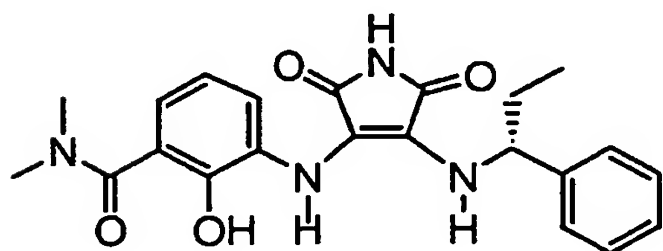
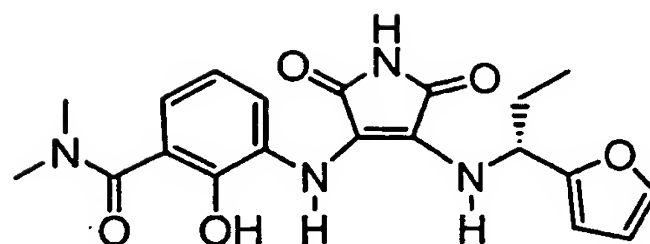
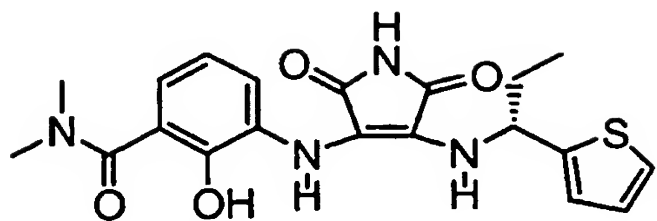
In another embodiment of this invention, R¹⁵ in formula I is selected from the group consisting of: H, methyl, aryl and cyclohexyl.

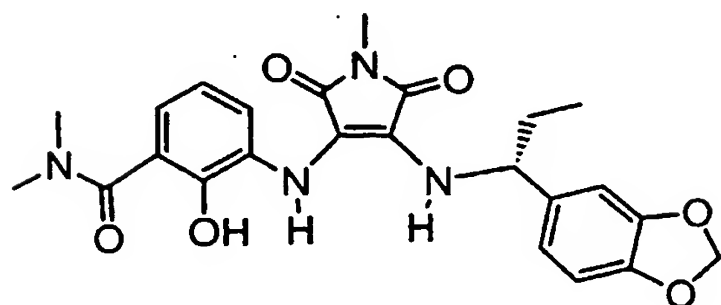
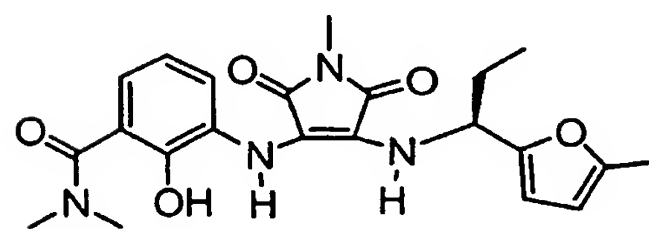
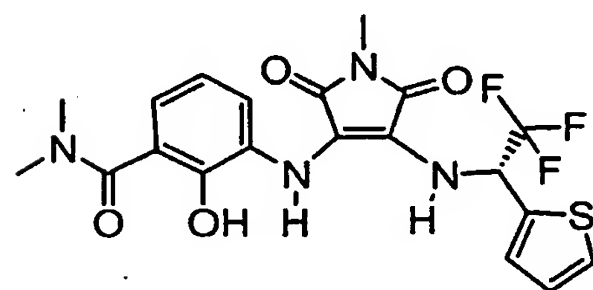
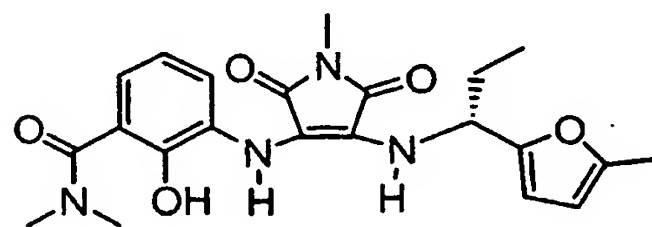
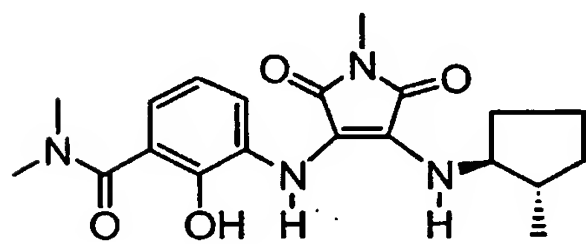
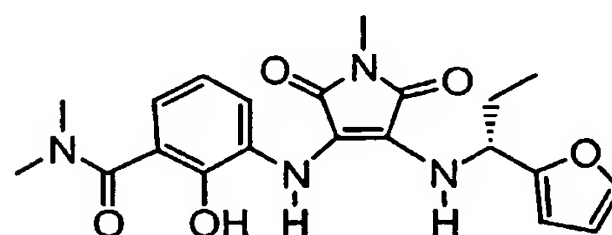
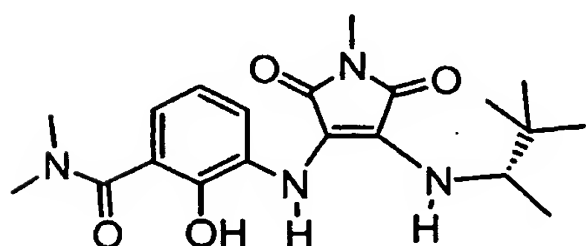
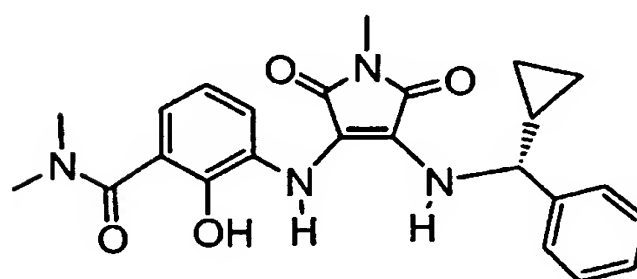
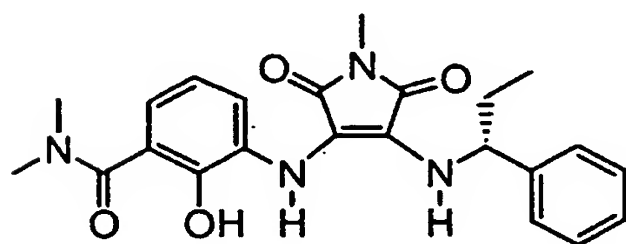
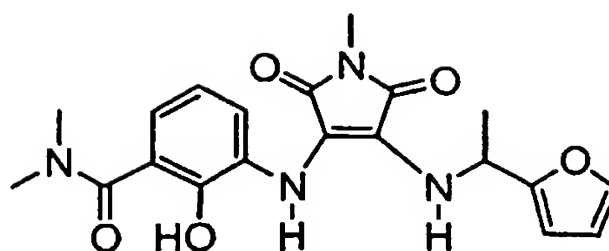
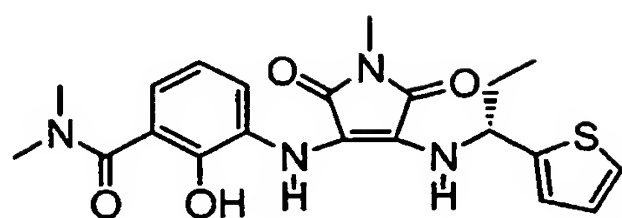
Other embodiments of this invention are directed to the pharmaceutically acceptable salts of the compounds of formula I.

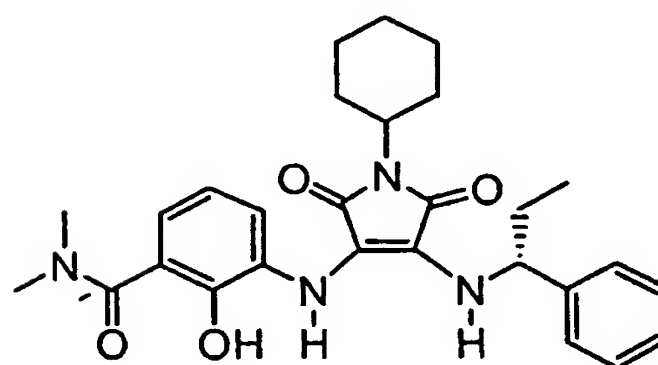
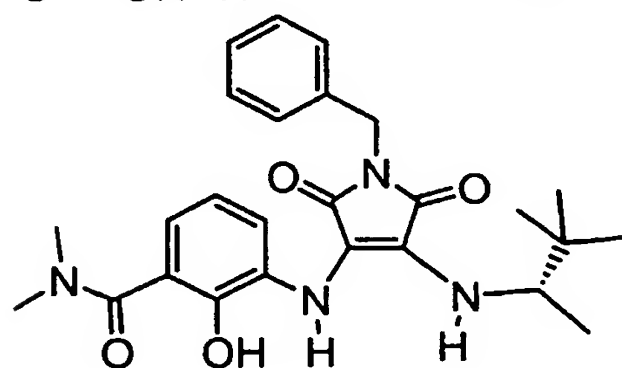
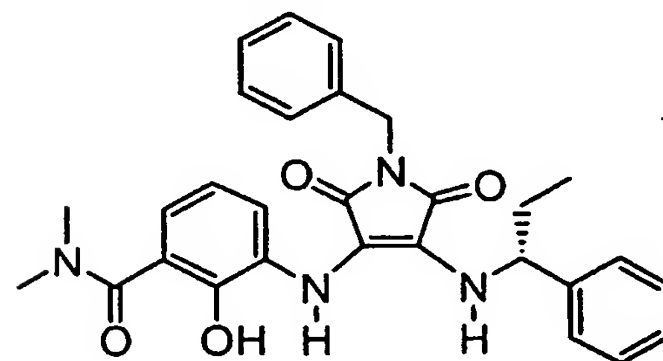
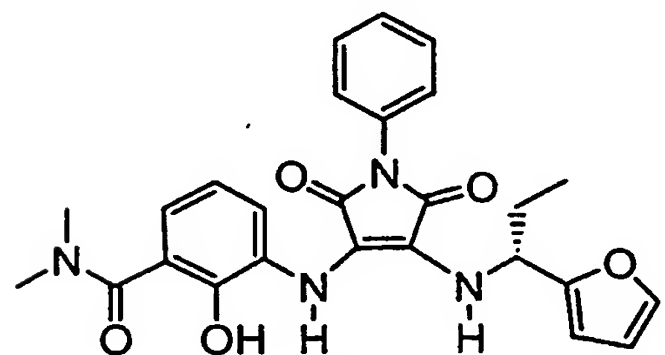
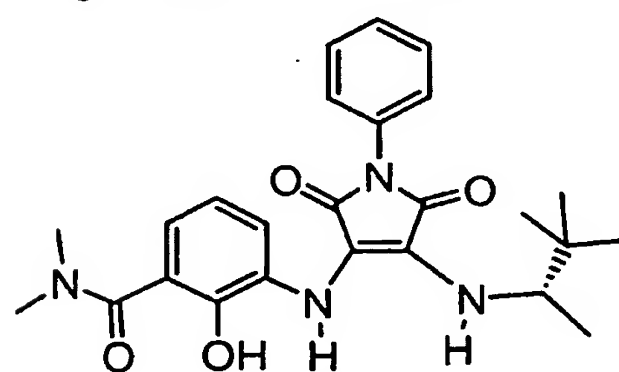
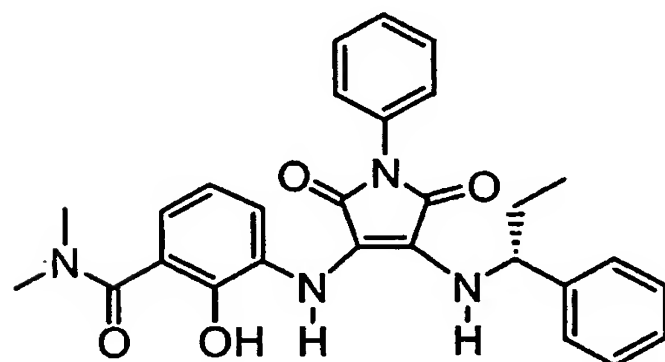
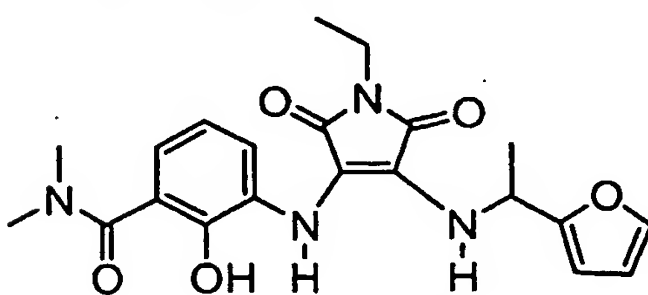
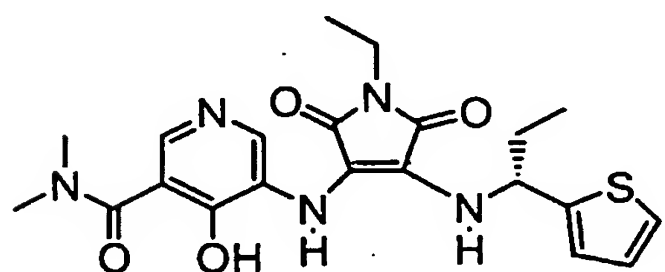
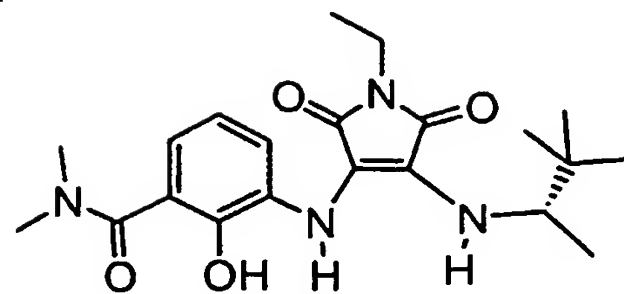
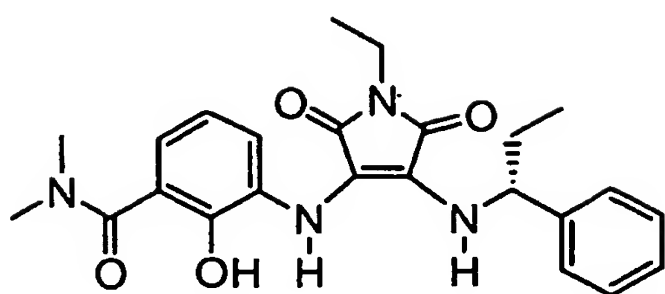
- 5 Other embodiments of this invention are directed to the sodium salts of the compounds of formula I.

Other embodiments of this invention are directed to the calcium salts of the compounds of formula I.

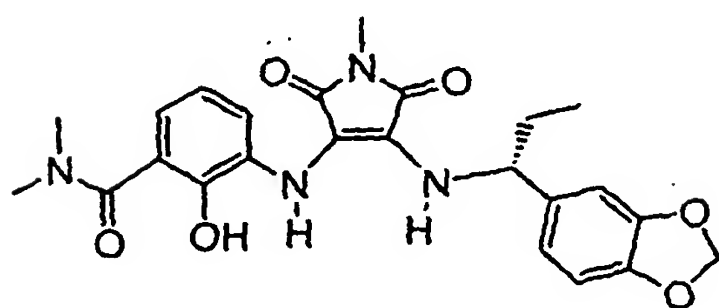
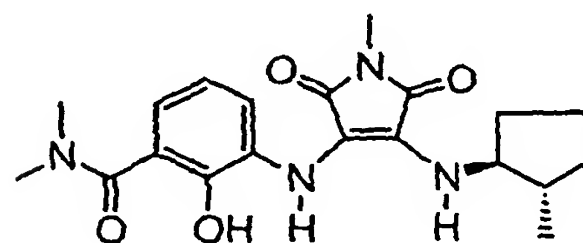
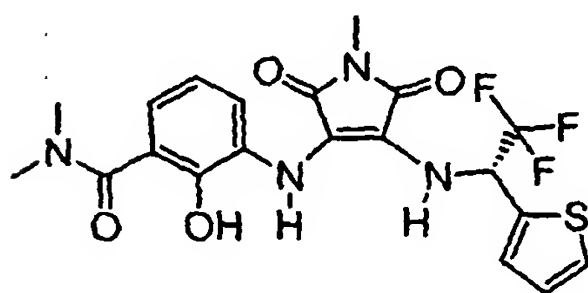
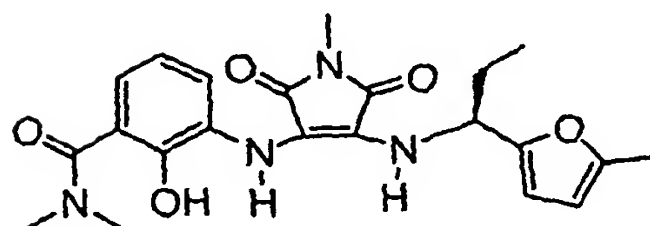
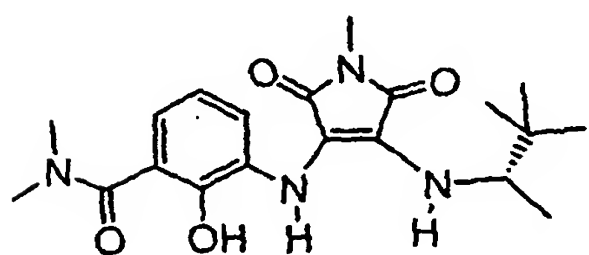
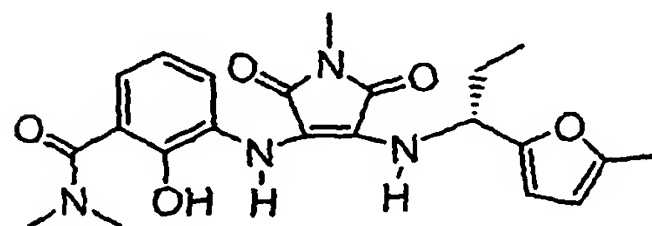
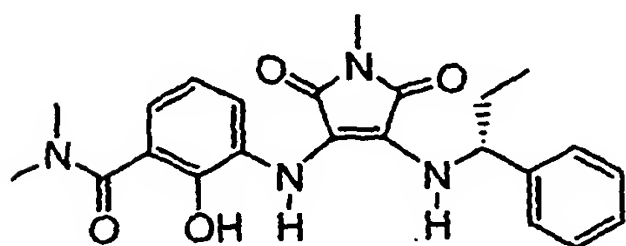
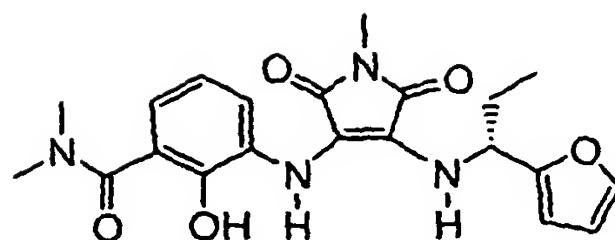
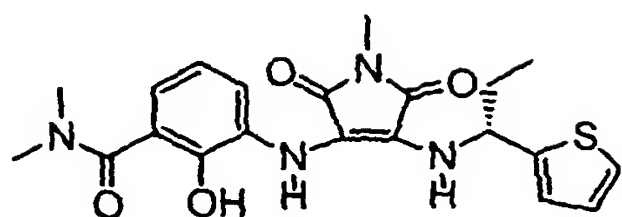
Preferred compounds of the invention are listed below:

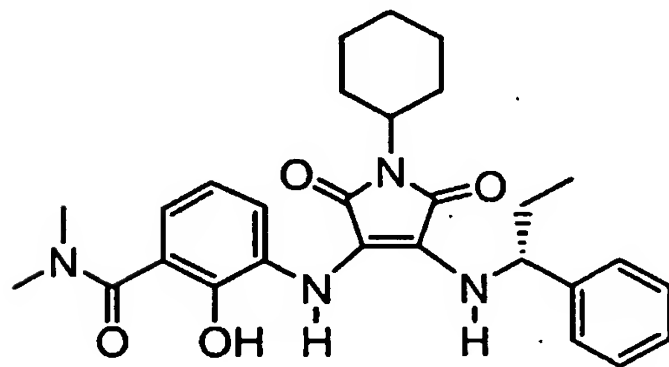
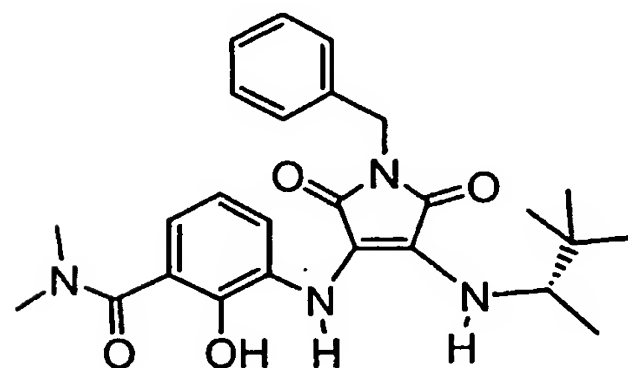
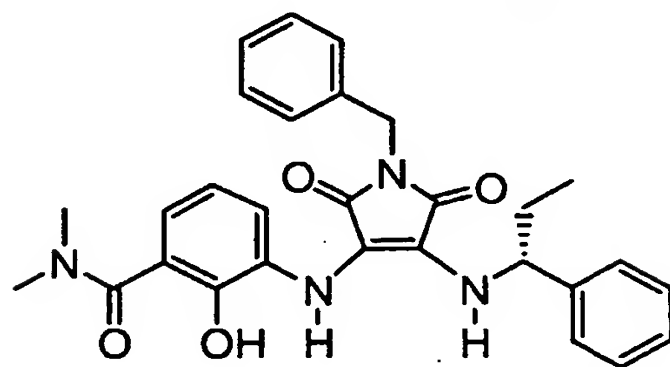
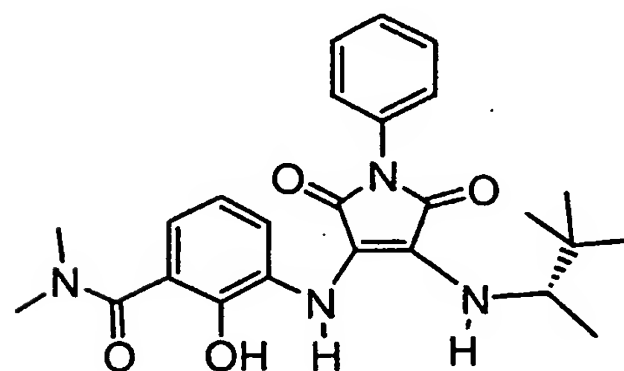
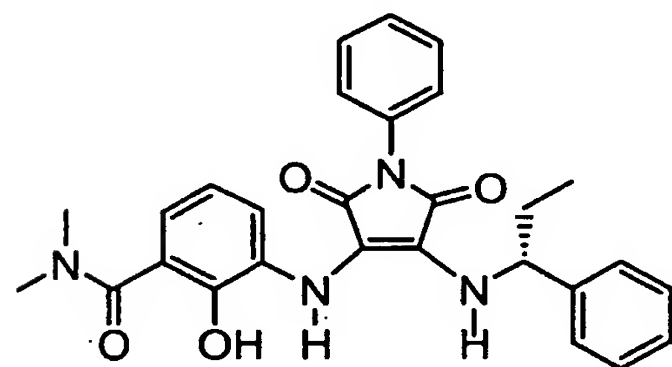
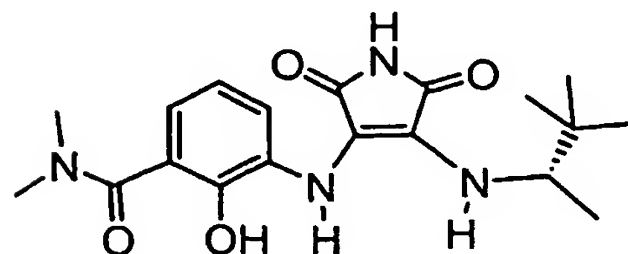
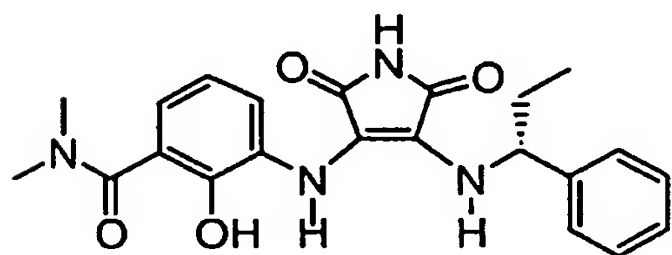
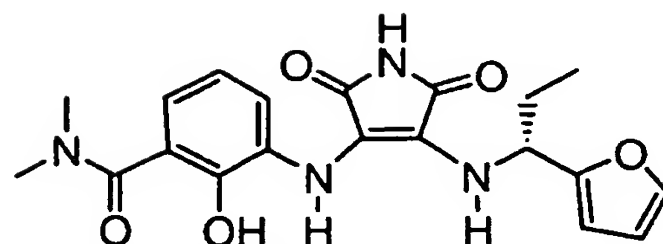
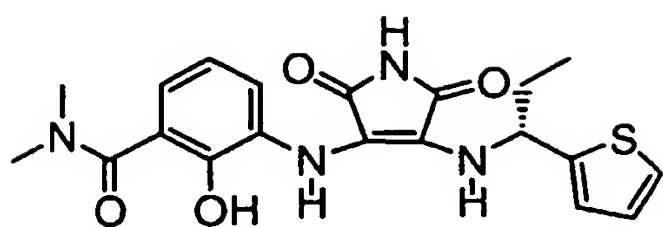




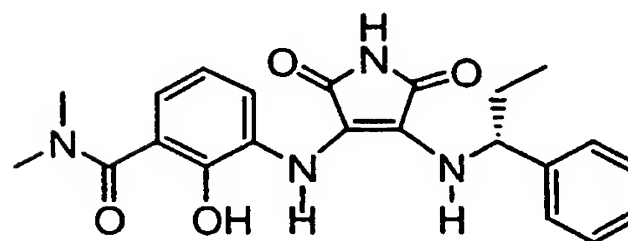
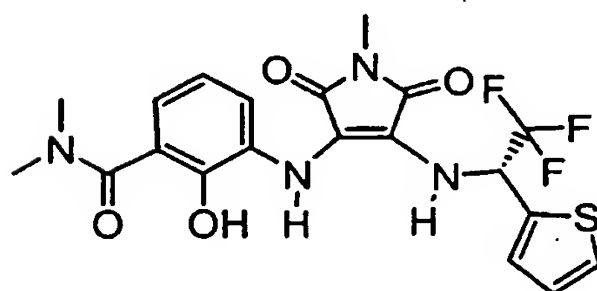
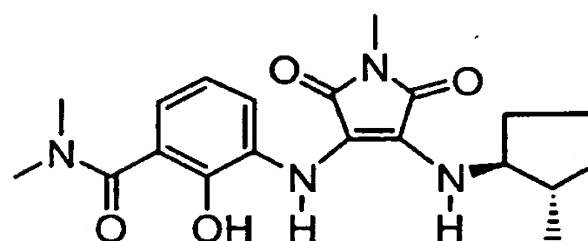
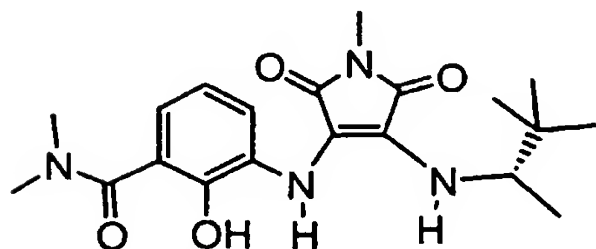
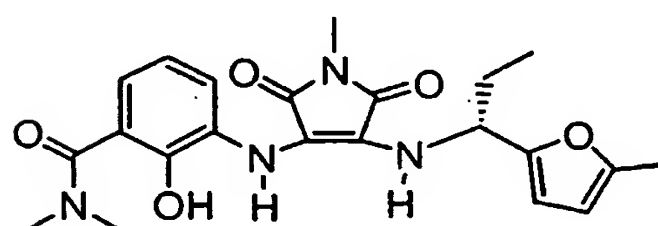
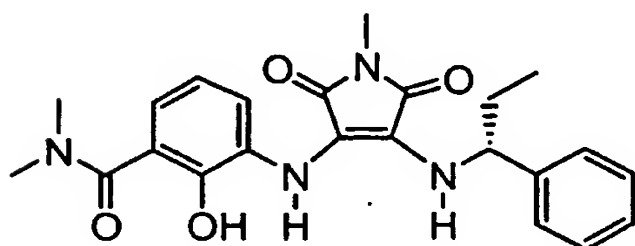
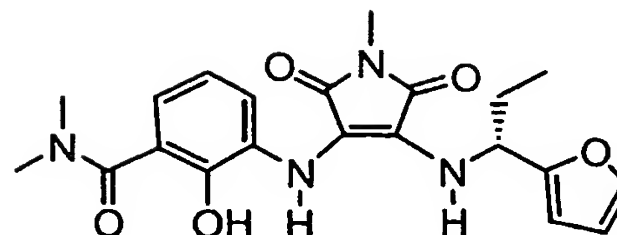
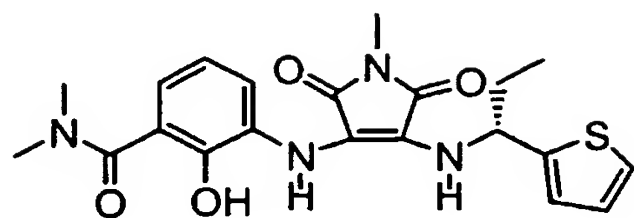


More preferred compounds of the invention are listed below:





A most preferred group of compounds of the invention is listed below:



For compounds of the invention having at least one asymmetrical carbon atom, all isomers, including diastereomers, enantiomers and rotational isomers are contemplated as being part of this invention. The invention includes *d* and *l* isomers in both pure form and in admixture, including racemic mixtures. Isomers can be prepared using conventional techniques, or by separating isomers of a compound of formula (I).

Compounds of formula (I) can exist in unsolvated and solvated forms, including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like, are equivalent to the unsolvated forms for purposes of this invention.

A compound of formula (I) may form pharmaceutically acceptable salts with organic and inorganic acids or bases. Examples of suitable bases for salt formation include but are not limited to sodium hydroxide, lithium hydroxide, potassium hydroxide, and calcium hydroxide. Salts of phenols can be made by heating acidic compounds with any of the above mentioned bases according to procedures well known to those skilled in the art. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those skilled in the art. The salts are prepared by contacting the free base forms with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution, such as dilute aqueous sodium hydroxide, lithium hydroxide, potassium hydroxide, calcium hydroxide, potassium carbonate, ammonia or sodium bicarbonate. The neutral forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the salts are otherwise equivalent to their respective neutral forms for purposes of the invention.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g., magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), Remington: The Science and Practice of Pharmacy, 20th Edition, (2000), Lippincott Williams & Wilkins, Baltimore, MD.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, *e.g.*, nitrogen.

Also included are solid form preparations that are intended to be converted,
5 shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal composition can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir
10 type as are conventional in the art for this purpose.

The compounds of the invention may also be delivered by direct application to the tumor site following surgery, *e.g.*, in a sponge preparation.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such
15 form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, *e.g.*, an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.01 mg to about 1000 mg, preferably from about 0.01 mg to
20 about 750 mg, more preferably from about 0.01 mg to about 500 mg, and most preferably from about 0.01 mg to about 250 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated.
25 Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated
30 according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 0.04 mg/day to about 4000 mg/day, in two to four divided doses.

Examples of chemokine mediated disease include: psoriasis, atopic dermatitis, asthma, COPD, adult respiratory disease, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, stroke, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer's disease, graft vs. host reaction, allograft rejections, malaria, acute respiratory distress syndrome, delayed type hypersensitivity reaction, atherosclerosis, cerebral and cardiac ischemia, osteoarthritis, multiple sclerosis, restinosis, angiogenesis, osteoporosis, gingivitis, respiratory viruses, herpes viruses, hepatitis viruses, HIV, Kaposi's sarcoma associated virus, meningitis, cystic fibrosis, pre-term labor, cough, pruritis, multi-organ dysfunction, trauma, strains, sprains, contusions, psoriatic arthritis, herpes, encephalitis, CNS vasculitis, traumatic brain injury, CNS tumors, subarachnoid hemorrhage, post surgical trauma, interstitial pneumonitis, hypersensitivity, crystal induced arthritis, acute and chronic pancreatitis, acute alcoholic hepatitis, necrotizing enterocolitis, chronic sinusitis, angiogenic ocular disease, ocular inflammation, retinopathy of prematurity, diabetic retinopathy, macular degeneration with the wet type preferred and corneal neovascularization, polymyositis, vasculitis, acne, gastric and duodenal ulcers, celiac disease, esophagitis, glossitis, airflow obstruction, airway hyperresponsiveness, bronchiectasis, bronchiolitis, bronchiolitis obliterans, chronic bronchitis, cor pulmonae, cough, dyspnea, emphysema, hypercapnea, hyperinflation, hypoxemia, hyperoxia-induced inflammations, hypoxia, surgical lung volume reduction, pulmonary fibrosis, pulmonary hypertension, right ventricular hypertrophy, peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD), granulocytic ehrlichiosis, sarcoidosis, small airway disease, ventilation-perfusion mismatching, wheeze, colds, gout, alcoholic liver disease, lupus, burn therapy, periodontitis, transplant reperfusion injury and early transplantation.

Another aspect of the invention is a method treating cancer, comprising administering to a patient in need thereof, concurrently or sequentially, a therapeutically effective amount of (a) a compound of formula (I) and (b) a chemotherapeutic agent (i.e. an antineoplastic agent, microtubule affecting agent or anti-angiogenesis agent).

In an embodiment of the invention, a compound of formula (I) is combined with one of the following antineoplastic agents: gemcitabine, paclitaxel (Taxol®), 5-

Fluorouracil (5-FU), cyclophosphamide (Cytosan®), temozolomide, taxotere or Vincristine.

5 Classes of compounds that can be used as the chemotherapeutic agent (antineoplastic agent) include: alkylating agents, antimetabolites, natural products and their derivatives, hormones, anti-hormones, anti-angiogenic agents and steroids (including synthetic analogs), and synthetics. Examples of compounds within these classes are given below.

10 Alkylating agents (including nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas and triazenes): Uracil mustard, Chloromethine, Cyclophosphamide (Cytosan®), Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylene-melamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, and Temozolomide.

15 Antimetabolites (including folic acid antagonists, pyrimidine analogs, purine analogs and adenosine deaminase inhibitors): Methotrexate, 5-Fluorouracil, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, Pentostatine, and Gemcitabine.

20 Natural products and their derivatives (including vinca alkaloids, antitumor antibiotics, enzymes, lymphokines and epipodophyllotoxins): Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, paclitaxel (paclitaxel is commercially available as Taxol® and is described in more detail below in the subsection entitled "Microtubule Affecting Agents"), Mithramycin, Deoxyco-formycin, Mitomycin-C, L-Asparaginase, Interferons (especially IFN- α), Etoposide, and Teniposide.

25 Hormones and steroids (including synthetic analogs): 17 α -Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Tamoxifen, Methylprednisolone, Methyl-testosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, Zoladex.

30 Synthetics (including inorganic complexes such as platinum coordination complexes): Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, and Hexamethylmelamine.

 Anti-angiogenic agents include Marimastat, AG3340, Col-3, Neovastat, BMS-275291, Thalidomide, Squalamine, Endostatin, SU-5416, SU-6668,

Interferon-alpha, Anti-VEGF antibody, EMD121974, CAI, Interleukin-12, IM862, Platelet Factor-4, Vitaxin, Angiostatin, Suramin, TNP-470, PTK-787, ZD-6474, ZD-101, Bay 129566, CGS27023A, taxotere and Taxol.

5 Methods for the safe and effective administration of most of these
chemotherapeutic agents are known to those skilled in the art. In addition, their
administration is described in the standard literature. For example, the
administration of many of the chemotherapeutic agents is described in the
"Physicians' Desk Reference" (PDR), e.g., 1996 edition (Medical Economics
Company, Montvale, NJ 07645-1742, USA); the disclosure of which is incorporated
10 herein by reference thereto.

As used herein, a microtubule affecting agent is a compound that interferes
with cellular mitosis, *i.e.*, having an anti-mitotic effect, by affecting microtubule
formation and/or action. Such agents can be, for instance, microtubule stabilizing
agents or agents which disrupt microtubule formation.

15 Microtubule affecting agents useful in the invention are well known to those
of skill in the art and include, but are not limited to allocolchicine (NSC 406042),
Halichondrin B (NSC 609395), colchicine (NSC 757), colchicine derivatives (e.g.,
NSC 33410), dolastatin 10 (NSC 376128), maytansine (NSC 153858), rhizoxin
(NSC 332598), paclitaxel (Taxol[®], NSC 125973), Taxol[®] derivatives (e.g.,
20 derivatives (e.g., NSC 608832), thiocolchicine (NSC 361792), trityl cysteine (NSC
83265), vinblastine sulfate (NSC 49842), vincristine sulfate (NSC 67574),
epothilone A, epothilone, and discodermolide (see Service, (1996) *Science*,
274:2009) estramustine, nocodazole, MAP4, and the like. Examples of such
agents are also described in the scientific and patent literature, see, e.g., Bulinski
25 (1997) *J. Cell Sci.* 110:3055-3064; Panda (1997) *Proc. Natl. Acad. Sci. USA*
94:10560-10564; Muhlradt (1997) *Cancer Res.* 57:3344-3346; Nicolaou (1997)
Nature 387:268-272; Vasquez (1997) *Mol. Biol. Cell.* 8:973-985; Panda (1996) *J.*
Biol. Chem. 271:29807-29812.

Particularly preferred agents are compounds with paclitaxel-like activity.
30 These include, but are not limited to paclitaxel and paclitaxel derivatives (paclitaxel-
like compounds) and analogues. Paclitaxel and its derivatives are available
commercially. In addition, methods of making paclitaxel and paclitaxel derivatives
and analogues are well known to those of skill in the art (see, e.g., U.S. Patent Nos:
5,569,729; 5,565,478; 5,530,020; 5,527,924; 5,508,447; 5,489,589; 5,488,116;

5,484,809; 5,478,854; 5,478,736; 5,475,120; 5,468,769; 5,461,169; 5,440,057; 5,422,364; 5,411,984; 5,405,972; and 5,296,506).

More specifically, the term "paclitaxel" as used herein refers to the drug commercially available as Taxol[®] (NSC number: 125973). Taxol[®] inhibits eukaryotic cell replication by enhancing polymerization of tubulin moieties into stabilized microtubule bundles that are unable to reorganize into the proper structures for mitosis. Of the many available chemotherapeutic drugs, paclitaxel has generated interest because of its efficacy in clinical trials against drug-refractory tumors, including ovarian and mammary gland tumors (Hawkins (1992) *Oncology*, 6: 17-23, Horwitz (1992) *Trends Pharmacol. Sci.* 13: 134-146, Rowinsky (1990) *J. Natl. Canc. Inst.* 82: 1247-1259).

Additional microtubule affecting agents can be assessed using one of many such assays known in the art, e.g., a semiautomated assay which measures the tubulin-polymerizing activity of paclitaxel analogs in combination with a cellular assay to measure the potential of these compounds to block cells in mitosis (see Lopes (1997) *Cancer Chemother. Pharmacol.* 41:37-47).

Generally, activity of a test compound is determined by contacting a cell with that compound and determining whether or not the cell cycle is disrupted, in particular, through the inhibition of a mitotic event. Such inhibition may be mediated by disruption of the mitotic apparatus, e.g., disruption of normal spindle formation. Cells in which mitosis is interrupted may be characterized by altered morphology (e.g., microtubule compaction, increased chromosome number, etc.).

In a preferred embodiment, compounds with possible tubulin polymerization activity are screened *in vitro*. In a preferred embodiment, the compounds are screened against cultured WR21 cells (derived from line 69-2 wap-ras mice) for inhibition of proliferation and/or for altered cellular morphology, in particular for microtubule compaction. *In vivo* screening of positive-testing compounds can then be performed using nude mice bearing the WR21 tumor cells. Detailed protocols for this screening method are described by Porter (1995) *Lab. Anim. Sci.*, 45(2):145-150.

Other methods of screening compounds for desired activity are well known to those of skill in the art. Typically such assays involve assays for inhibition of microtubule assembly and/or disassembly. Assays for microtubule assembly are described, for example, by Gaskin *et al.* (1974) *J. Molec. Biol.*, 89: 737-758. U.S.

Patent No. 5,569,720 also provides *in vitro* and *in vivo* assays for compounds with paclitaxel-like activity.

Methods for the safe and effective administration of the above-mentioned microtubule affecting agents are known to those skilled in the art. In addition, their administration is described in the standard literature. For example, the administration of many of the chemotherapeutic agents is described in the "Physicians' Desk Reference" (PDR), e.g., 1996 edition (Medical Economics Company, Montvale, NJ 07645-1742, USA); the disclosure of which is incorporated herein by reference thereto.

The amount and frequency of administration of the compounds of formula (I) and the chemotherapeutic agents and/or radiation therapy will be regulated according to the judgment of the attending clinician (physician) considering such factors as age, condition and size of the patient as well as severity of the disease being treated. A dosage regimen of the compound of formula (I) can be oral administration of from 10 mg to 2000 mg/day, preferably 10 to 1000 mg/day, more preferably 50 to 600 mg/day, in two to four (preferably two) divided doses, to block tumor growth. Intermittent therapy (e.g., one week out of three weeks or three out of four weeks) may also be used.

The chemotherapeutic agent and/or radiation therapy can be administered according to therapeutic protocols well known in the art. It will be apparent to those skilled in the art that the administration of the chemotherapeutic agent and/or radiation therapy can be varied depending on the disease being treated and the known effects of the chemotherapeutic agent and/or radiation therapy on that disease. Also, in accordance with the knowledge of the skilled clinician, the therapeutic protocols (e.g., dosage amounts and times of administration) can be varied in view of the observed effects of the administered therapeutic agents (i.e., antineoplastic agent or radiation) on the patient, and in view of the observed responses of the disease to the administered therapeutic agents.

In the methods of this invention, a compound of formula (I) is administered concurrently or sequentially with a chemotherapeutic agent and/or radiation. Thus, it is not necessary that, for example, the chemotherapeutic agent and the compound of formula (I), or the radiation and the compound of formula (I), should be administered simultaneously or essentially simultaneously. The advantage of a

simultaneous or essentially simultaneous administration is well within the determination of the skilled clinician.

Also, in general, the compound of formula (I) and the chemotherapeutic agent do not have to be administered in the same pharmaceutical composition, and may, because of different physical and chemical characteristics, have to be administered by different routes. For example, the compound of formula (I) may be administered orally to generate and maintain good blood levels thereof, while the chemotherapeutic agent may be administered intravenously. The determination of the mode of administration and the advisability of administration, where possible, in the same pharmaceutical composition, is well within the knowledge of the skilled clinician. The initial administration can be made according to established protocols known in the art, and then, based upon the observed effects, the dosage, modes of administration and times of administration can be modified by the skilled clinician.

The particular choice of a compound of formula (I), and chemo-therapeutic agent and/or radiation will depend upon the diagnosis of the attending physicians and their judgement of the condition of the patient and the appropriate treatment protocol.

The compound of formula (I), and chemotherapeutic agent and/or radiation may be administered concurrently (e.g., simultaneously, essentially simultaneously or within the same treatment protocol) or sequentially, depending upon the nature of the proliferative disease, the condition of the patient, and the actual choice of chemotherapeutic agent and/or radiation to be administered in conjunction (i.e., within a single treatment protocol) with the compound of formula (I).

If the compound of formula (I) and the chemotherapeutic agent and/or radiation are not administered simultaneously or essentially simultaneously, then the initial order of administration of the compound of formula (I) and the chemotherapeutic agent and/or radiation, may not be important. Thus, the compound of formula (I) may be administered first followed by the administration of the chemotherapeutic agent and/or radiation; or the chemo-therapeutic agent and/or radiation may be administered first followed by the administration of the compound of formula (I). This alternate administration may be repeated during a single treatment protocol. The determination of the order of administration, and the number of repetitions of administration of each therapeutic agent during a treatment protocol, is well within the knowledge of the skilled physician after evaluation of the

disease being treated and the condition of the patient. For example, the chemotherapeutic agent and/or radiation may be administered first, especially if it is a cytotoxic agent, and then the treatment continued with the administration of a compound of formula (I) followed, where determined advantageous, by the administration of the chemotherapeutic agent and/or radiation, and so on until the treatment protocol is complete.

Thus, in accordance with experience and knowledge, the practicing physician can modify each protocol for the administration of a component (therapeutic agent-- *i.e.*, the compound of formula (I), chemotherapeutic agent or radiation) of the treatment according to the individual patient's needs, as the treatment proceeds.

The attending clinician, in judging whether treatment is effective at the dosage administered, will consider the general well-being of the patient as well as more definite signs such as relief of disease-related symptoms, inhibition of tumor growth, actual shrinkage of the tumor, or inhibition of metastasis. Size of the tumor can be measured by standard methods such as radio-logical studies, *e.g.*, CAT or MRI scan, and successive measurements can be used to judge whether or not growth of the tumor has been retarded or even reversed. Relief of disease-related symptoms such as pain, and improvement in overall condition can also be used to help judge effectiveness of treatment.

BIOLOGICAL EXAMPLES

The compounds of the present invention are useful in the treatment of CXC-chemokine mediated conditions and diseases. This utility is manifested in their ability to inhibit IL-8 and GRO- α chemokine which may be demonstrated by the following *in vitro* assays.

Receptor Binding Assays:

CXCR1 SPA Assay

For each well of a 96 well plate, a reaction mixture of 10 μ g hCXCR1-CHO overexpressing membranes (Biosignal) and 200 μ g/well WGA-SPA beads (Amersham) in 100 μ l is prepared in CXCR1 assay buffer (25 mM HEPES, pH 7.8, 2 mM CaCl_2 , 1mM MgCl_2 , 125 mM NaCl, 0.1% BSA) (Sigma). A 0.4 nM stock of ligand, [^{125}I]-IL-8 (NEN) is prepared in the CXCR1 assay buffer. 20X stock

solutions of test compounds are prepared in DMSO (Sigma). A 6 X stock solution of IL-8 (R&D) is prepared in CXCR2 assay buffer. The above solutions are added to a 96-well assay plate (PerkinElmer) as follows: 10 μ l test compound or DMSO, 40 μ l CXCR1 assay buffer or IL-8 stock, 100 μ l of reaction mixture, 50 μ l of ligand stock (Final [Ligand] = 0.1 nM). The assay plates are shaken for 5 minutes on plate shaker, then incubated for 8 hours before cpm/well are determined in Microbeta Trilux counter (PerkinElmer). % Inhibition of Total binding-NSB (250 nM IL-8) is determined for IC₅₀ values.

10 Alternative CXCR1 SPA Assay

Protocol using CXCR1-expressing membranes from Biosignal Packard

For each 50 μ l reaction, a working stock of 0.25 μ g/ μ l hCXCR1-CHO over-expressing membranes with a specific activity of 0.05 pmol/mg (Biosignal Packard) and 25 μ g/ μ l WGA-SPA beads (Perkin Elmer Life Sciences) is prepared in CXCR1 assay buffer (25 mM HEPES, pH 7.8, 0.1 mM CaCl₂, 1mM MgCl₂, 100 mM NaCl) (Sigma). This mixture is incubated on ice for 30 minutes and then centrifuged at 2500 rpm for 5 minutes. The beads and membranes are resuspended in CXCR1 assay buffer to the same concentrations as in the original mixture. A 0.125 nM stock of ligand, [¹²⁵I]-IL-8 (Perkin Elmer Life Sciences), is prepared in the CXCR1 assay buffer. Test compounds are first serially diluted by half-logs in DMSO (Sigma) and then diluted 20-fold in CXCR1 assay buffer. The above solutions are added to a Corning NBS (non-binding surface) 96-well assay plate as follows: 20 μ l test compound or 5% DMSO (final [DMSO] = 2%), 20 μ l of membranes and SPA bead mixture (Final [membrane] = 5 μ g/reaction; Final [SPA bead] = 500 μ g/reaction), 10 μ l of ligand stock (Final [¹²⁵I]-IL-8] = 0.025 nM). The assay plates are incubated for 4 hours before cpm/well are determined in a Microbeta Trilux counter (Perkin Elmer Life Sciences). IC₅₀ values are quantified using nonlinear regression analysis in GraphPad Prism.

30 Alternative CXCR1 SPA Assay

Protocol using CXCR1-expressing membranes from Euroscreen

For each 50 μ l reaction, a working stock of 0.025 μ g/ μ l hCXCR1-CHO over-expressing membranes with a specific activity of 3.47 pmol/mg (Euroscreen) and 5

$\mu\text{g}/\mu\text{l}$ WGA-SPA beads (Perkin Elmer Life Sciences) is prepared in CXCR1 assay buffer (25 mM HEPES, pH 7.8, 2.0 mM CaCl_2 , 1mM MgCl_2 , 125 mM NaCl) (Sigma). This mixture is incubated on ice for 5 minutes. A 0.125 nM stock of ligand, [^{125}I]-IL-8 (Perkin Elmer Life Sciences), is prepared in the CXCR1 assay buffer. Test compounds are first serially diluted by half-logs in DMSO (Sigma) and then diluted 13.3-fold in CXCR1 assay buffer. The above solutions is added to a Corning NBS (non-binding surface) 96-well assay plate as follows: 20 μl test compound or 7.5% DMSO (final [DMSO] = 3%), 20 μl of membranes and SPA bead mixture (Final [membrane] = 0.5 $\mu\text{g}/\text{reaction}$; Final [SPA bead] = 100 $\mu\text{g}/\text{reaction}$), 10 μl of ligand stock (Final [^{125}I]-IL-8] = 0.025 nM). The assay plates are incubated for 4 hours before cpm/well are determined in a Microbeta Trilux counter (Perkin Elmer Life Sciences). IC_{50} values are quantified using nonlinear regression analysis in GraphPad Prism.

15 CXCR2 SPA Assay

For each well of a 96 well plate, a reaction mixture of 4 μg hCXCR2-CHO overexpressing membranes (Biosignal) and 200 $\mu\text{g}/\text{well}$ WGA-SPA beads (Amersham) in 100 μl is prepared in CXCR2 assay buffer (25 mM HEPES, pH 7.4, 2 mM CaCl_2 , 1mM MgCl_2). A 0.4 nM stock of ligand, [^{125}I]-IL-8 (NEN), is prepared in the CXCR2 assay buffer. 20X stock solutions of test compounds are prepared in DMSO (Sigma). A 6 X stock solution of GRO- α (R&D) is prepared in CXCR2 assay buffer. The above solutions are added to a 96-well assay plate (PerkinElmer or Corning) as follows: 10 μl test compound or DMSO, 40 μl CXCR2 assay buffer or GRO- α stock, 100 μl of reaction mixture, 50 μl of ligand stock (Final [Ligand] = 0:1 nM). When 40 X stock solutions of test compounds in DMSO are prepared, then the above protocol is used except instead 5 μl test compound or DMSO and 45 μl CXCR2 assay buffer are used. The assay plates are shaken for 5 minutes on a plate shaker, then incubated for 2-8 hours before cpm/well are determined in Microbeta Trilux counter (PerkinElmer). % Inhibition of total binding minus non-specific binding (250 nM Gro- α or 50 μM antagonist) is determined and IC_{50} values calculated.

Alternative CXCR2 SPA AssayProtocol using the CXCR2 50 μ l assay

For each 50 μ l reaction, a working stock of 0.031 μ g/ μ l hCXCR2-CHO over-expressing membranes with a specific activity of 0.4 pmol/mg (Biosignal Packard) and 2.5 μ g/ μ l WGA-SPA beads (Perkin Elmer Life Sciences) is prepared in CXCR2 assay buffer (25 mM HEPES, pH 7.4, 2.0 mM CaCl_2 , 1 mM MgCl_2) (Sigma). This mixture is incubated on ice for 5 minutes. A 0.50 nM stock of ligand, [^{125}I]-IL-8 (Perkin Elmer Life Sciences), is prepared in the CXCR2 assay buffer. Test compounds are first serially diluted by half-logs in DMSO (Sigma) and then diluted 13.3-fold in CXCR2 assay buffer. The above solutions are added to a Corning NBS (non-binding surface) 96-well assay plate as follows: 20 μ l test compound or 7.5% DMSO (final [DMSO] = 3%), 20 μ l of membranes and SPA bead mixture (final [membrane] = 0.625 μ g/reaction; final [SPA bead] = 50 μ g/reaction), 10 μ l of ligand stock (final [^{125}I]-IL-8] = 0.10 nM). The assay plates are incubated for 2 hours before cpm/well are determined in a Microbeta Trilux counter (Perkin Elmer Life Sciences). IC₅₀ values are quantified using nonlinear regression analysis in GraphPad Prism.

Alternative CXCR2 SPA AssayProtocol using the CXCR2 200 μ l assay

For each 200 μ l reaction, a working stock of 0.02 μ g/ μ l hCXCR2-CHO over-expressing membranes with a specific activity of 0.6 pmol/mg (Biosignal Packard) and 2 μ g/ μ l WGA-SPA beads (Perkin Elmer Life Sciences) is prepared in CXCR2 assay buffer (25 mM HEPES, pH 7.4, 2.0 mM CaCl_2 , 1 mM MgCl_2) (Sigma). This mixture is incubated on ice for 5 minutes. A 0.40 nM stock of ligand, [^{125}I]-IL-8 (Perkin Elmer Life Sciences), is prepared in the CXCR2 assay buffer. Test compounds are first serially diluted by half-logs in DMSO (Sigma) and then diluted 20-fold in CXCR2 assay buffer. The above solutions are added to a Corning NBS (non-binding surface) 96-well assay plate as follows: 50 μ l test compound or 10% DMSO (final [DMSO] = 2.5%), 100 μ l of membranes and SPA bead mixture (final [membrane] = 2 μ g/reaction; final [SPA bead] = 200 μ g/reaction), 50 μ l of ligand stock (final [^{125}I]-IL-8] = 0.10 nM). The assay plates are incubated for 2 hours before cpm/well were determined in a Microbeta Trilux counter (Perkin Elmer Life

Sciences). IC_{50} values are quantified using nonlinear regression analysis in GraphPad Prism.

Calcium Fluorescence Assay (FLIPR)

5 HEK 293 cells stably transfected with hCXCR2 and $G\alpha_i/q$ are plated at 10,000 cells per well in a Poly-D-Lysine Black/Clear plate (Becton Dickinson) and incubated 48 hours at 5% CO_2 , 37°C. The cultures are then incubated with 4 mM fluo-4, AM (Molecular Probes) in Dye Loading Buffer (1% FBS, HBSS w. Ca & Mg, 20 mM HEPES (Cellgro), Probenicid (Sigma)) for 1 hour. The cultures are washed
10 with wash buffer (HBSS w Ca, & Mg, 20 mM HEPES, Probenicid (2.5 mM)) three times, then 100 μ l/well wash buffer is added.

During incubation, compounds are prepared as 4X stocks in 0.4% DMSO (Sigma) and wash buffer and added to their respective wells in the first addition plate. IL-8 or GRO- α (R&D Systems) concentrations are prepared 4X in wash buffer
15 + 0.1% BSA and added to their respective wells in second addition plate.

Culture plate and both addition plates are then placed in the FLIPR imaging system to determine change in calcium fluorescence upon addition of compound and then ligand. Briefly, 50 μ l of compound solutions or DMSO solution is added to respective wells and change in calcium fluorescence measured by the FLIPR for
20 1 minute. After a 3 minute incubation within the instrument, 50 μ l of ligand is then added and the change in calcium fluorescence measured by the FLIPR instrument for 1 minute. The area under each stimulation curve is determined and values used to determine % Stimulation by compound (agonist) and % Inhibition of Total Calcium response to ligand (0.3 nM IL-8 or GRO- α) for IC_{50} values of the test
25 compounds.

Chemotaxis assays for 293-CXCR2

A chemotaxis assay is setup using Fluoroblok inserts (Falcon) for 293-CXCR2 cells (HEK-293 cells overexpressing human CXCR2). The standard protocol used at present is as follows:

- 30
1. Inserts are coated with collagenIV (2 μ g/ml) for 2 hrs at 37°C.
 2. The collagen is removed and inserts are allowed to air dry overnight.
 3. Cells are labeled with 10 μ M calcein AM (Molecular Probes) for 2 hrs. Labeling is done in complete media with 2% FBS.

4. Dilutions of compound are made in minimal media (0.1% BSA) and placed inside the insert which is positioned inside the well of a 24 well plate. Within the well is IL-8 at a concentration of 0.25nM in minimal media. Cells are washed and resuspended in minimal media and placed inside the insert at a concentration of 50,000 cells per insert.

5. Plate is incubated for 2hrs and inserts are removed and placed in a new 24 well. Fluorescence is detected at excitation=485 nM and emission=530 nM.

Cytotoxicity Assays

A cytotoxicity assay for CXCR2 compounds is conducted on 293-CXCR2 cells. Concentrations of compounds are tested for toxicity at high concentrations to determine if they may be used for further evaluation in binding and cell based assays. The protocol is as follows:

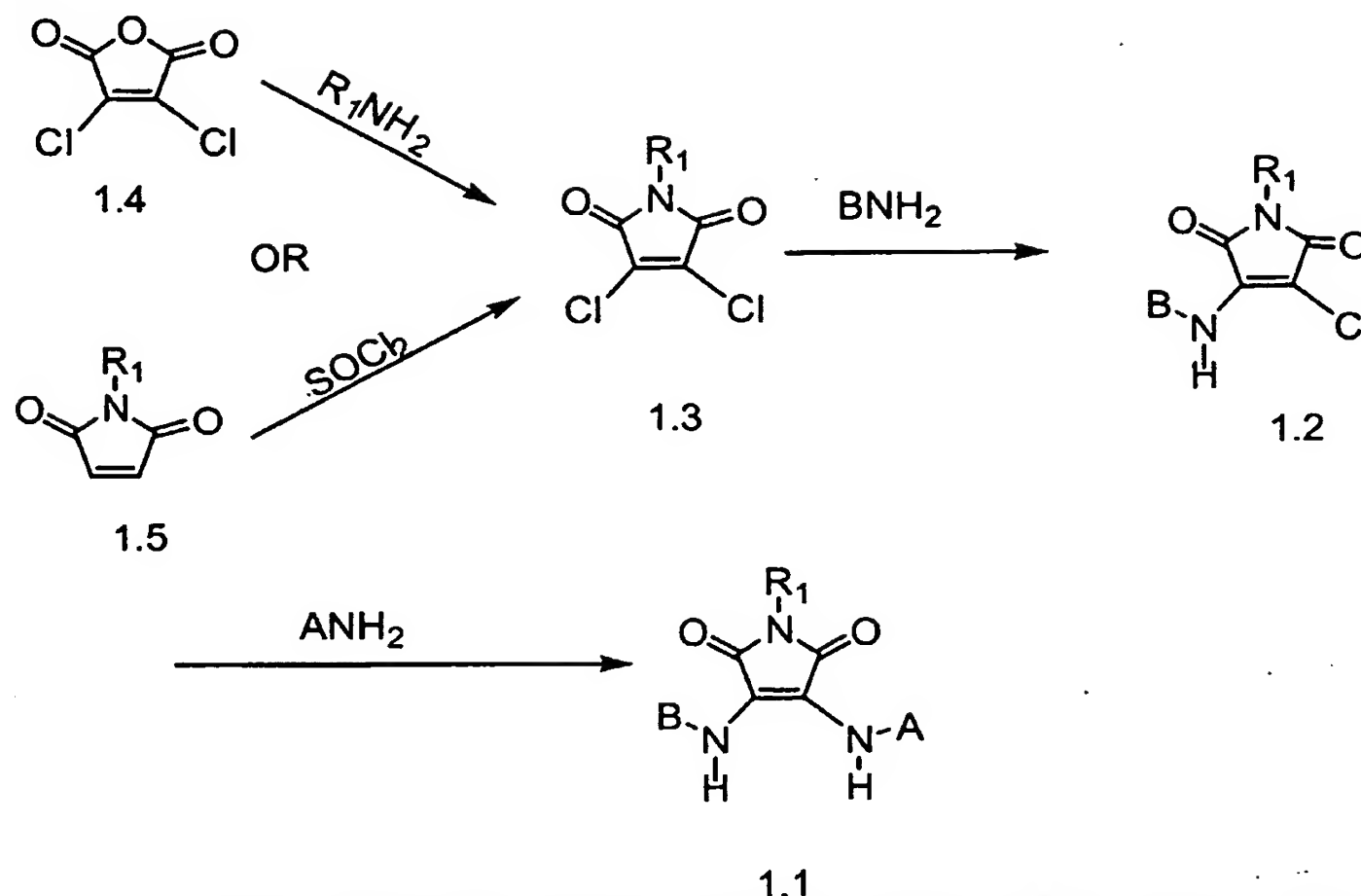
1. 293-CXCR2 cells are plated overnight at a concentration of 5000 cells per well in complete media.
2. Dilutions of compound are made in minimal media w/0.1% BSA. Complete media is poured off and the dilutions of compound are added. Plates are incubated for 4, 24 and 48hrs. Cells are labeled with 10uM calcein AM for 15 minutes to determine cell viability. Detection method is the same as above.

Soft Agar Assay

10,000 SKMEL-5 cells/well are placed in a mixture of 1.2% agar and complete media with various dilutions of compound. Final concentration of agar is 0.6%. After 21 days viable cell colonies are stained with a solution of MTT (1mg/ml in PBS). Plates are then scanned to determine colony number and size. IC₅₀ is determined by comparing total area vs. compound concentration.

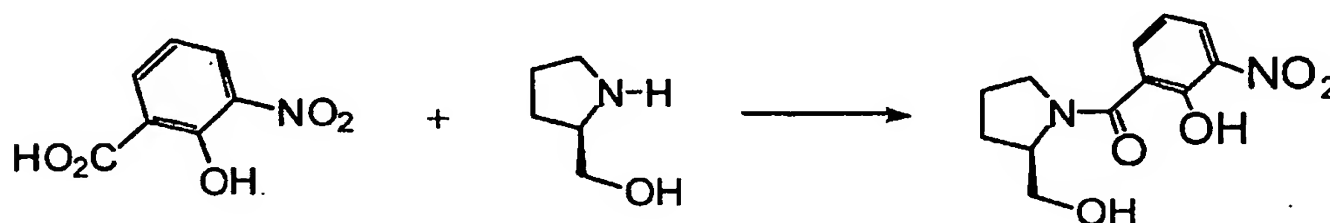
Compounds of this invention may exhibit a range of CXCR2 receptor binding activities from about 1 nM to about 10,000 nM.

Compounds of formula (I) may be produced by processes known to those skilled in the art in the following reaction schemes and in the preparations and examples below.

Scheme 1

If one were to follow the procedure set forth in Bioorg. Med. Chem. 1999, 7, 1067-1074 starting with compound 1.4 or the procedure set forth in Acta Crystallogr. Sect. C: Cryst. Struct. Commun. 2000, 56, 190-192 starting with compound 1.5, one would obtain the compound 1.3; compound 1.3 could react with an amine BNH_2 to afford compound 1.2 and then compound 1.2 could react with another amine ANH_2 to afford the compound 1.1.

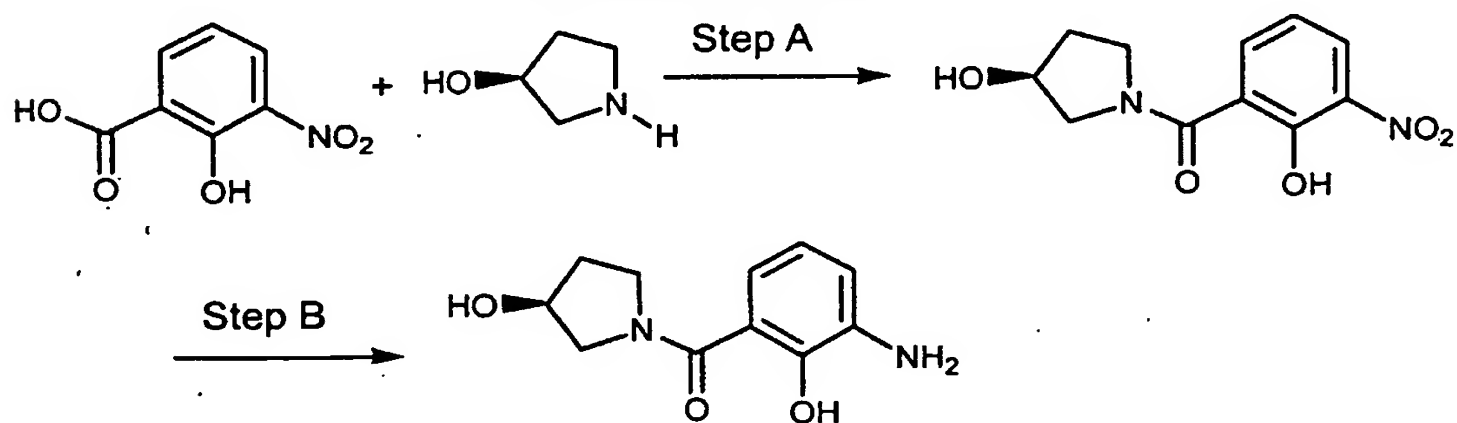
The following examples illustrate the preparation of some of the compounds of the invention and are not to be construed as limiting the invention disclosed herein. Alternate mechanistic pathways and analogous structures will be apparent to those skilled in the art.

PREPARATIVE EXAMPLE 1

71

3-Nitrosalicylic acid (500 mg, 2.7 mmol), DCC (563 mg) and ethyl acetate (10 mL) were combined and stirred for 10 min. (R)-(-)-2-pyrrolidinemethanol (0.27 mL) was added and the resulting suspension was stirred at room temperature overnight. The solid was filtered and the filtrate washed with 1N NaOH. The aqueous phase was acidified and extracted with EtOAc. The resulting organic phase was dried over anhydrous MgSO_4 , filtered and concentrated in vacuo. Purification of the residue by preparative plate chromatography (silica gel, 5% MeOH/ CH_2Cl_2 saturated with AcOH) gave the above compound (338 mg, 46%, $\text{MH}^+ = 267$).

PREPARATIVE EXAMPLE 2



Step A

3-Nitrosalicylic acid (9.2 g), bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP, 23 g) and N,N-diisopropylethylamine (DIEA, 26 mL) in anhydrous CH_2Cl_2 (125 mL) were combined and stirred at 25°C for 30 min. (R)-(+)-3-pyrrolidinol (8.7 g) in CH_2Cl_2 (25 mL) was added over 25 min and the resulting suspension was stirred at room temperature overnight. The mixture was extracted with 1M NaOH (aq) and the organic phase was discarded. The aqueous phase was acidified with 1M HCl (aq), extracted with EtOAc, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to afford the crude product (7 g) which was used without further purification.

Step B

The crude product from Step A above was stirred with 10% Pd/C (0.7 g) in MeOH (100 mL) under a hydrogen gas atmosphere overnight. The reaction mixture was filtered through celite, the filtrate concentrated in vacuo, and the resulting

residue purified by column chromatography (silica gel, 10% MeOH/CH₂Cl₂ saturated with NH₄OH) to give the product (2.5 g, 41%, MH⁺=223).

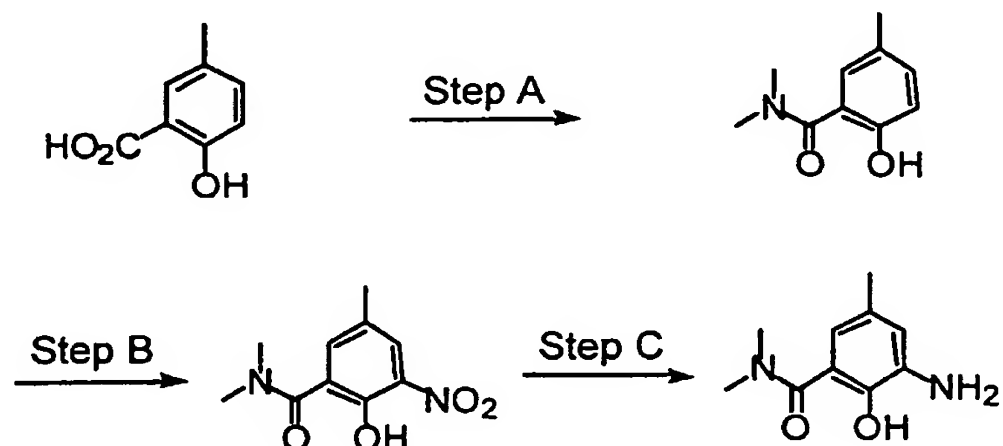
PREPARATIVE EXAMPLE 3-12

- 5 Following the procedures set forth in Preparative Examples 1-2 but using the carboxylic acid, amine, and appropriate coupling agent [DCC (Prep. Ex. 1) or PyBroP (Prep. Ex. 2)] listed in the Table below, the amide product was obtained and used without further purification.

Prep Ex.	Carboxylic acid	Amine	Amide Product	1. Coupling Agent 2. Yield 3. MH ⁺
3				1. PyBroP 2. 87%, 86% 3. 181
4				1. PyBroP 2. 49% 3. 209
6		NH ₃		1. PyBroP 2. 95% 3. 153
7		—NH ₂		1. PyBroP 2. 83% 3. 167
8				1. PyBroP 2. 76% 3. 223
11				1. PyBroP 2. 59%, 69% 3. 207

12				1. PyBroP 2. 49%, 86% 3. 237
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PREPARATIVE EXAMPLE 15



5 Step A

Following a similar procedure as in Preparative Example 1 except substituting dimethylamine (2M in THF, 33 mL) for (R)-(-)-2-pyrrolidinemethanol and 5-methylsalicylic acid (5 g) for 3-nitrosalicylic acid, the above compound was prepared (6.5g).

10

Step B

Nitric acid (0.8 mL) in H₂SO₄ was added to a cooled (-20°C) suspension of the title compound from Step A above (3 g) in H₂SO₄ (25 mL). The mixture was treated with 50% NaOH (aq) dropwise, extracted with CH₂Cl₂, dried over anhydrous MgSO₄, filtered and concentrated in vacuo to give the above compound as a crude solid (2.1 g, 44%, MH⁺ = 225).

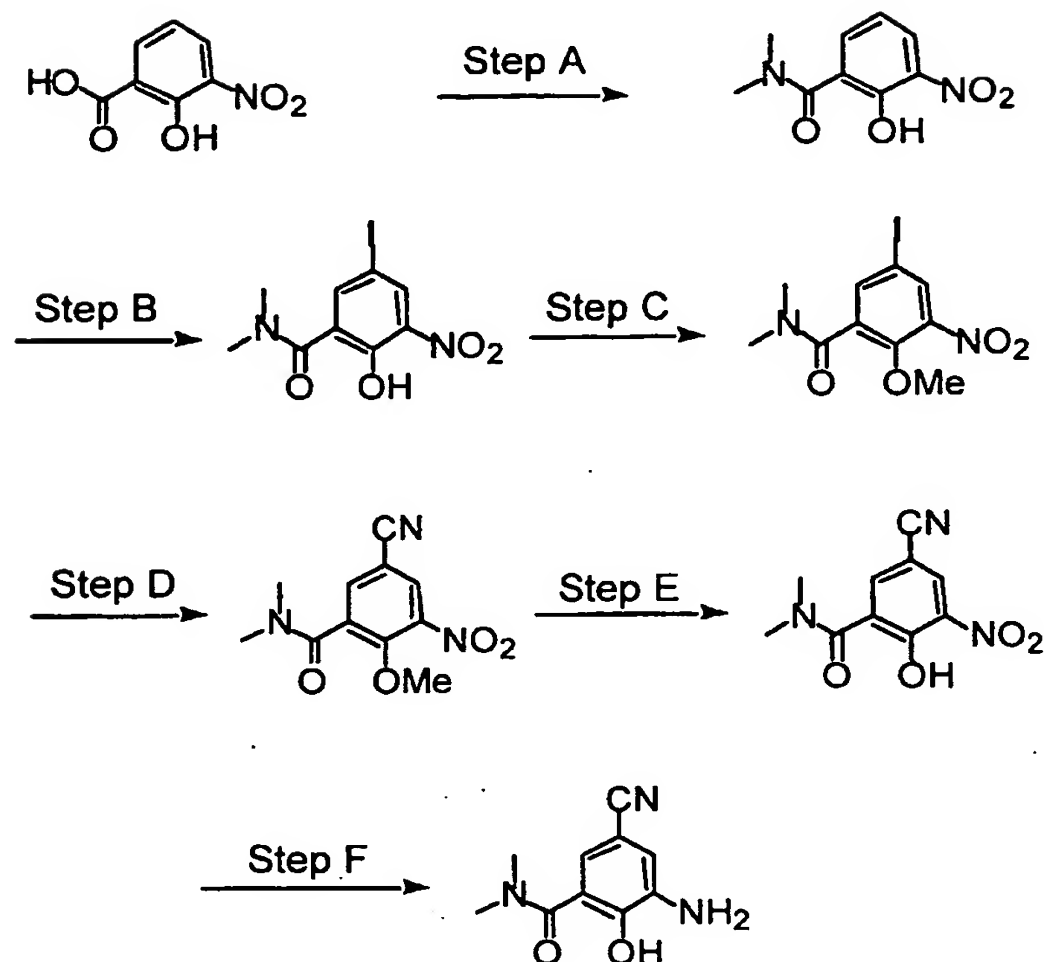
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Step C

The product was prepared following a similar procedure as described in Preparative Example 2, Step B (0.7 g, 99%, MH⁺ = 195).

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74
PREPARATIVE EXAMPLE 25



Step A

Following a similar procedure as in Preparative Example 2 Step A, except substituting dimethylamine for (R)-(-)-2-pyrrolidinemethanol, the product of step A was prepared.

Step B

The product from step A above (8 g) was combined with iodine (9.7 g), silver sulfate (11.9 g), EtOH (200 mL) and water (20 mL) and stirred overnight. Filtration, concentration of the filtrate, re-dissolution in CH₂Cl₂ and washing with 1M HCl (aq) gave an organic solution which was dried over anhydrous MgSO₄, filtered and concentrated in vacuo to afford the product of step B (7.3 g, 57%, MH⁺ = 337).

Step C

The product from Step B above (3.1 g) was combined with DMF (50 mL) and MeI (0.6 mL). NaH (60% in mineral oil, 0.4 g) was added portionwise and the mixture was stirred overnight. Concentration in vacuo afforded a residue which was diluted with CH₂Cl₂, washed with 1M NaOH (aq), dried over anhydrous MgSO₄,

filtered and concentrated in vacuo. Purification through a silica gel column (EtOAc/Hex, 1:1) gave the product of step C (1.3 g, 41%, $MH^+ = 351$).

Step D

5 The product from Step C above (200 mg), $Zn(CN)_2$ (132 mg), $Pd(PPh_3)_4$ (130 mg) and DMF (5 mL) were heated at 80°C for 48 hrs, then cooled to room temperature and diluted with EtOAc and 2M NH_4OH . After shaking well, the organic extract was dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo and purified by preparative plate chromatography (Silica, EtOAc/Hex, 1:1) to give
10 the product of step D (62 mg, 44%, $MH^+ = 250$).

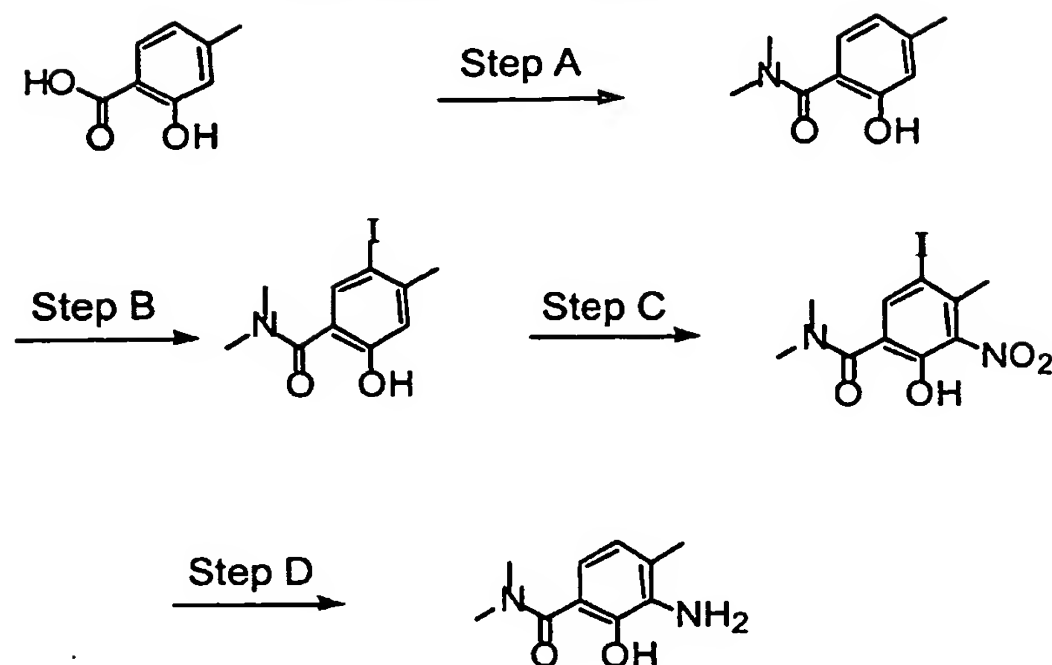
Step E

BBr_3 (1.3 mL, 1M in CH_2Cl_2) was added to a CH_2Cl_2 solution (5 mL) of the product from Step D above (160 mg) and stirred for 30 min. The mixture was
15 diluted with water, extracted with CH_2Cl_2 , dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give the product of step E (158 mg, $MH^+ = 236$).

Step F

 A mixture of the product from step E above (160 mg), platinum oxide (83%,
20 19 mg), and EtOH (20 mL) was stirred under hydrogen (25-40 psi) for 1.5 hr. Filtration through celite and concentration in vacuo afforded the product of step F (165 mg, $MH^+ = 206$).

76
PREPARATIVE EXAMPLE 26



Step A

Following a similar procedure as in Preparative Example 1 except substituting dimethylamine (2M in THF, 50 mL) for (R)-(-)-2-pyrrolidinemethanol and 4-methylsalicylic acid (15 g) for 3-nitrosalicylic acid, the product of step A was prepared (6.3 g, 35%).

Step B

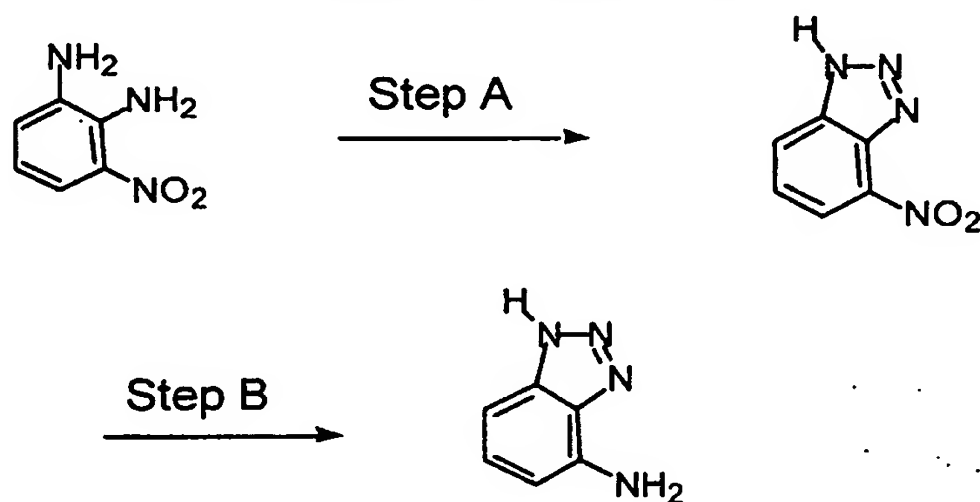
The product from step A above (1.5 g) was combined with iodine (2.1 g), NaHCO₃ (1.1 g), EtOH (40 mL) and water (10 mL) and stirred overnight. Filtration, concentration of the filtrate, re-dissolution in CH₂Cl₂ and washing with 1M HCl (aq) gave an organic solution which was dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Purification by flash column chromatography (silica gel, 0.5-0.7% MeOH/CH₂Cl₂) gave the product of step B (0.3 g, 57%, MH⁺ = 306).

Step C

Nitric acid (3.8 mL) in AcOH (10 mL) was added to the product from Step B above (0.8 g) and the mixture was stirred for 40 min. The mixture was diluted with water and extracted with CH₂Cl₂, dried over anhydrous MgSO₄, filtered and concentrated in vacuo to give the product of step C as a solid (0.8 g, 92%, MH⁺ = 351).

Step D

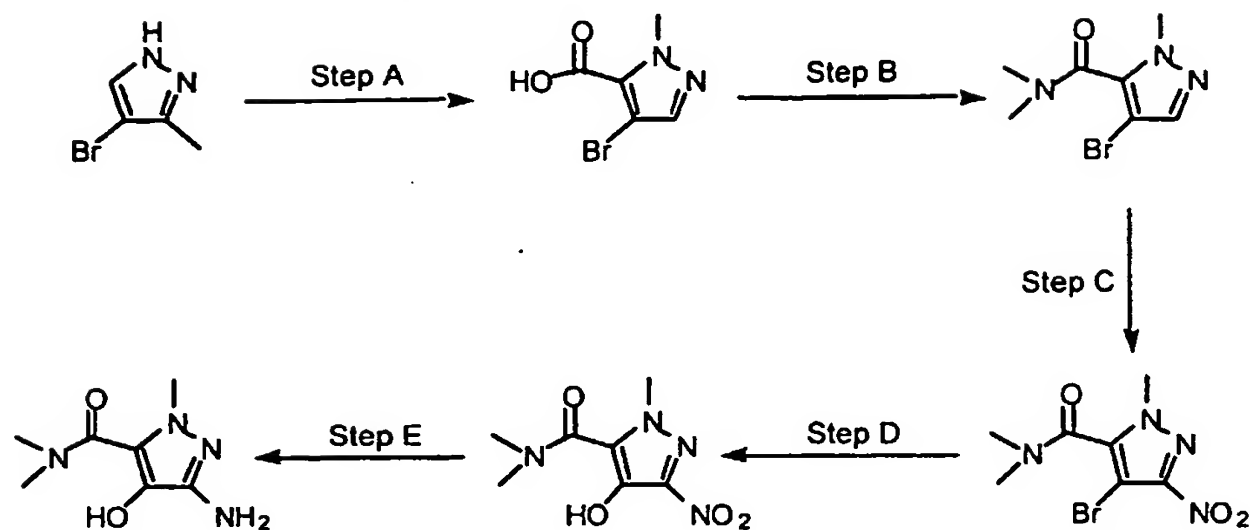
A mixture of the product from step C above (800 mg), 10% Pd/C (100 mg), and EtOH/MeOH (40 mL) was stirred in a parr shaker under hydrogen (45 psi) for 1.5 hr. Filtration through celite and concentration in vacuo afforded the title product after purification by preparative plate chromatography (Silica, 10% MeOH/CH₂Cl₂, saturated with NH₄OH) to give the product of step D (92 mg, 22%, MH⁺ = 195).

PREPARATIVE EXAMPLE 27Step A

3-Nitro-1,2-phenylenediamine (10 g), sodium nitrite (5.4 g) and acetic acid (20 mL) were heated at 60°C overnight, then concentrated in vacuo, diluted with water and extracted with EtOAc. The product precipitated from the organic phase (5.7 g) as a solid and was used directly in step B.

Step B

The product from Step A above (2.8 g) was stirred with 10% Pd/C (0.3 g) in MeOH (75 mL) under a hydrogen gas atmosphere overnight. The reaction mixture was filtered through celite and the filtrate concentrated in vacuo, to give the product (2.2 g, MH⁺=135).

PREPARATIVE EXAMPLE 28Step A

5 4-Bromopyrazole-3-carboxylic acid was prepared according to known methods, see: Yu. A. M.; Andreeva, M. A.; Perevalov, V. P.; Stepanov, V. I.; Dubrovskaya, V. A.; and Seraya, V. I. in Zh. Obs. Khim. (Journal of General Chemistry of the USSR) 1982, 52, 2592, and refs cited therein.

Step B

10 To a solution of 4-bromopyrazole-3-carboxylic acid (2.0 g), available from step A, in 65 mL of anhydrous DMF was added bromotripyrrolidinophosphonium hexafluorophosphate (PyBrop, 4.60 g), dimethyl amine (10 mL, 2.0 M in THF) and diisopropylethyl amine (5.2 mL) at 25 °C. The mixture was stirred for 26 h, and

15 concentrated under reduced pressure to an oily residue. This residue was treated with a 1.0 M NaOH aqueous solution, and extracted with ethyl acetate (4 x 50 mL). The organic extracts were combined, washed with brine, and dried with anhydrous Na₂SO₄. Removal of solvents yielded a yellowish oil, which was purified by preparative thin layer chromatography, eluting with CH₂Cl₂-MeOH (20:1), to give

20 1.09 g of the amide (48%, MH⁺ = 232.0).

Step C

25 To a solution of the amide (0.67 g), obtained from step B, in 8 mL of concentrated sulfuric acid at 0 °C was added potassium nitrate (1.16 g) in small portions. The cooling bath was removed and the mixture was heated at 110 °C for 6 h. After cooled to 25 °C, the mixture was poured into 80 mL of H₂O, and an

additional 20 mL of H₂O was used as rinsing. The aqueous mixture was extracted with CH₂Cl₂ (100 mL x 4). The combined extracts were washed with brine (50 mL), sat. NaHCO₃ aqueous solution (50 mL), brine (50 mL), and dried over Na₂SO₄. Evaporation of solvent gave a light yellow oil, which solidified on standing. The crude product was purified by flash column chromatography, eluting with CH₂Cl₂-MeOH (1:0, 50:1 and 40:1). Removal of solvents afforded 0.521 g (65%) of the product as a solid (MH⁺ = 277.1)

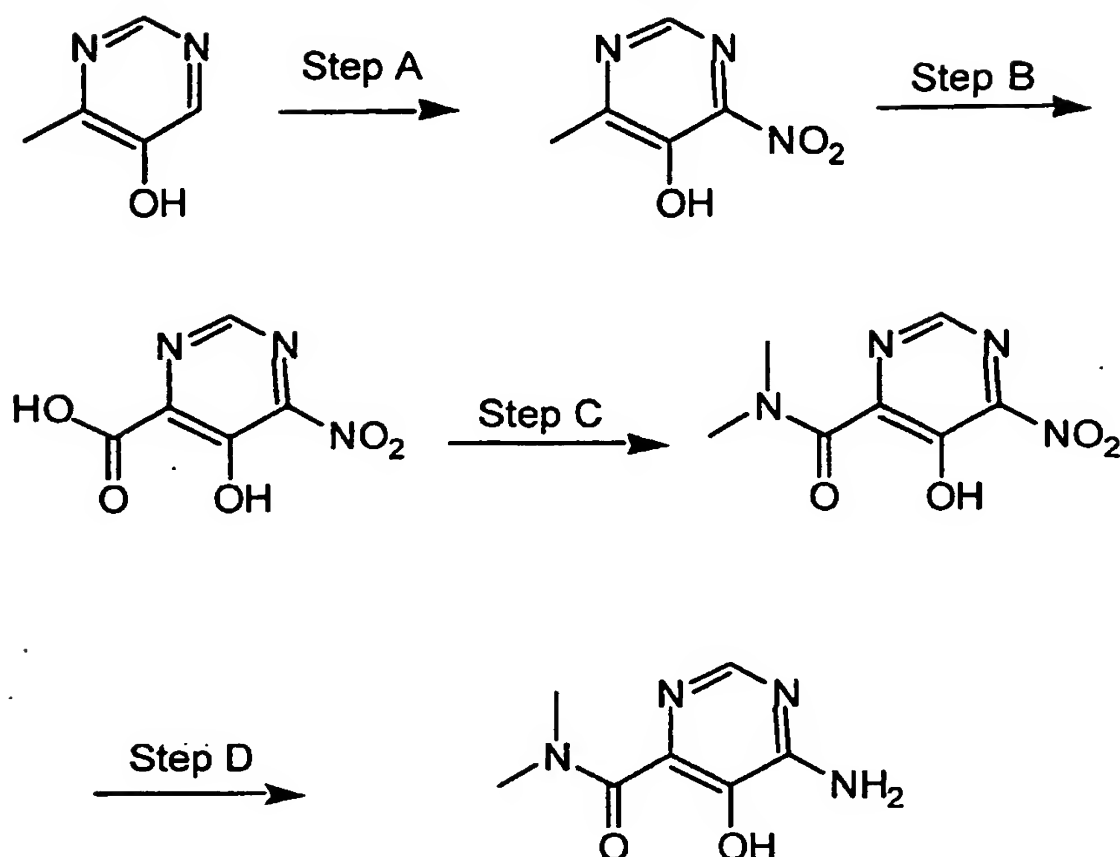
Step D

The product (61 mg) obtained from step C was dissolved in 3 mL of THF. To this solution at -78 °C was added dropwise along the inside wall of the flask a 1.6 M solution of n-butyl lithium in hexane. After 45 min, a solution of methyl borate (0.1 mL) in THF (1.0 mL) was added. After 1.5 h, a solution of acetic acid in THF (0.25 mL, 1:10 v/v) was added to the cold mixture. Stirring was continued for 10 min, and a 30 wt % aqueous hydrogen peroxide solution (0.1 mL) was added. An additional portion of hydrogen peroxide aqueous solution (0.05 mL) was added 20 min later. The cooling bath was removed, and the mixture was stirred at 25 °C for 36 h. The yellowish mixture was poured into 30 mL of H₂O, and the aqueous mixture was extracted with ethyl acetate (30 mL x 4). The extracts were combined, washed with brine (10 mL), 5% NaHCO₃ aqueous solution (10 mL) and brine (10 mL). The organic layer was dried with Na₂SO₄ and concentrated under reduced pressure to a yellow residue, which was purified by preparative thin layer chromatography eluting with CH₂Cl₂-MeOH (20:1) to give the hydroxylated product (5 mg, 10%, MH⁺ = 215.3).

Step E

If one were to treat the hydroxylated product of Step D with H₂ under the conditions of 10% palladium on carbon in ethanol, one would obtain the hydroxyl-amino compound.

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PREPARATIVE EXAMPLE 29



Step A

Following a similar procedure used in Preparative Example 26 Step C except
5 starting with the known compound, 4-methyl-pyrimidin-5-ol, the product of Step A
could be prepared.

Step B

Following a similar oxidation procedure used in Preparative Example 28 Step
10 A starting with the product from Step A above, the product of Step B could be
prepared.

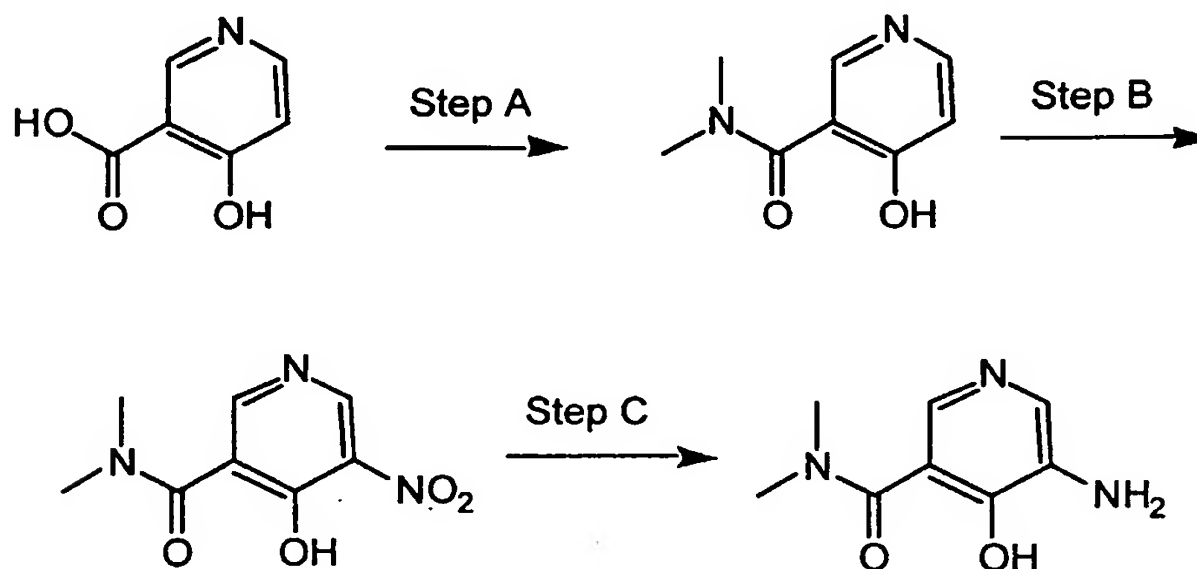
Step C

Following a similar procedure used in Preparative Example 15 Step A
15 starting with the product from Step B above, the product of Step C could be
prepared.

Step D

Following a similar procedure used in Preparative Example 25 Step F starting with the product of Step C above, the product of Step D could be prepared.

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PREPARATIVE EXAMPLE 30Step A

Following a similar procedure used in Preparative Example 15 Step A starting with the known 4-hydroxynicotinic acid, the product could be prepared.

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Step B

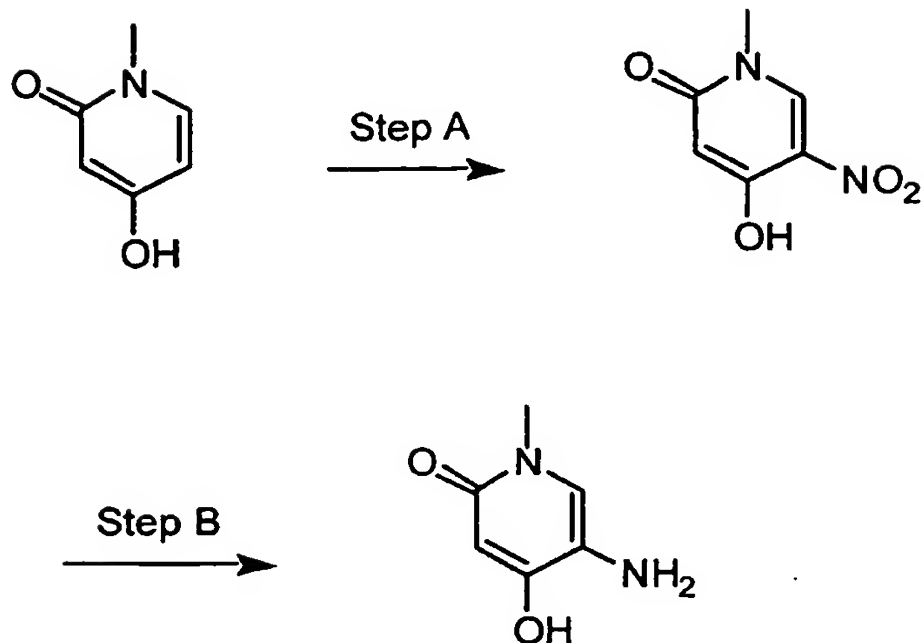
Following a similar procedure used in Preparative Example 26 Step C starting with the product from Step A above, the product of Step B could be prepared.

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Step C

Following a similar procedure used in Preparative Example 25 Step F starting with product from Step C above, the amine product could be prepared.

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PREPARATIVE EXAMPLE 31



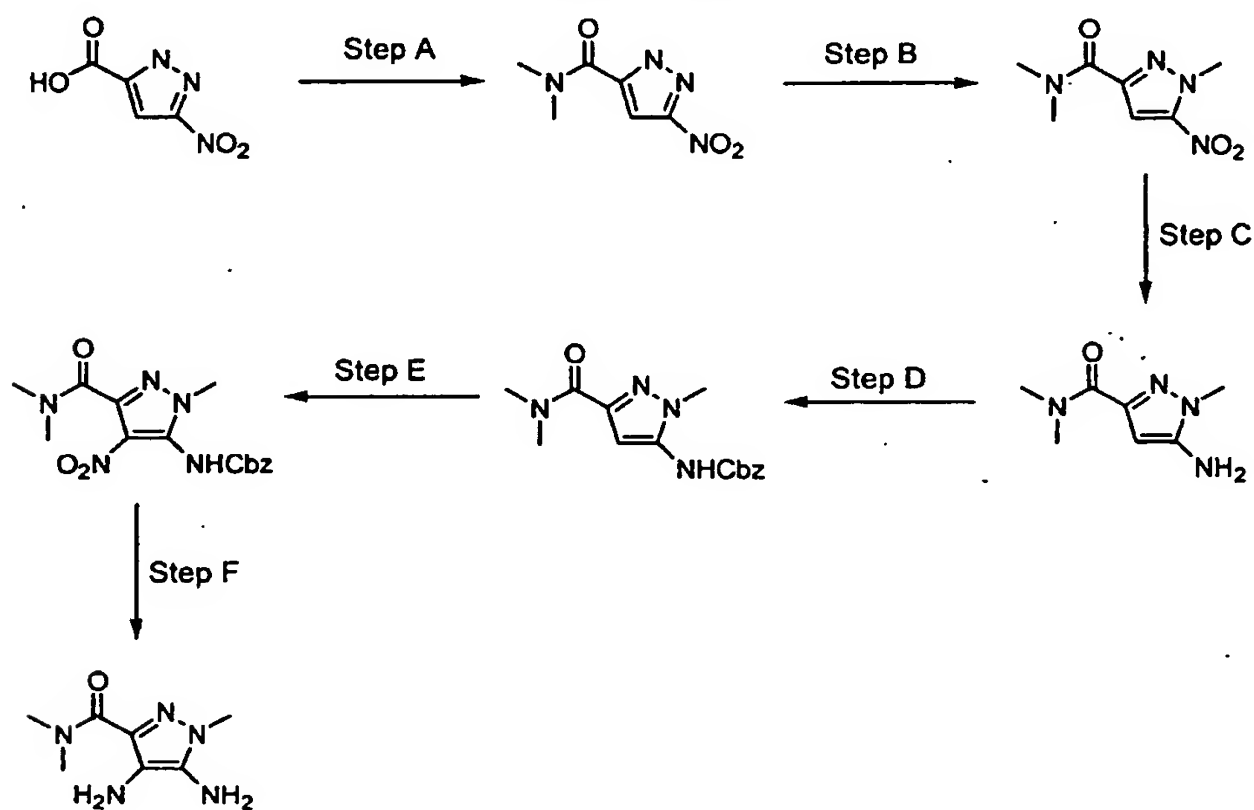
Step A

Following essentially the same procedure used in Preparative Example 26
5 Step C, the nitro product above could be prepared.

Step B

If one were to stir the nitro product from Step A above, a suitable Pt or Pd
10 catalyst and EtOH under hydrogen atmosphere (1-4 atm), one could obtain the amine product.

PREPARATIVE EXAMPLE 32



Step A

To a solution of 5-nitro-3-pyrazolecarboxylic acid (5.0 g, 31.83 mmol) in 160 mL of acetonitrile at room temperature was added bromotripyrrolidinophosphonium hexa-fluorophosphate (PyBrop, 14.9 g, 31.98 mmol) in small portions. A 2.0 M solution of dimethylamine in THF (40.0 mL, 80.0 mmol) was added to the mixture followed by a solution of diisopropylethylamine (14.0 mL, 80.2 mmol). After stirred for 36 h, the mixture was concentrated under reduced pressure to a residue, a mixture of solid and oil. Small volume of CH₂Cl₂ was added until all oily material was dissolved and fine colorless solid precipitated out. The solid was collected by filtration as the first crop of the product. The filtrate was concentrated to an oily residue which was treated with a mixture of CH₂Cl₂- hexanes (~1:1, v/v), and the colorless precipitation was filtered out as the second crop of the product. The combined solid product was further dried on high vacuum for several hours to afford 5.86 g (100%) of *N, N'*-dimethyl 5-nitro-3-pyrazolecarboxamide as a solid (MH⁺ = 185.0).

Step B

To a solution of *N, N'*-dimethyl 5-nitro-3-pyrazole amide (5.86 g, 31.83 mmol, available from step A) in 215 mL of anhydrous THF at room temperature was added solid lithium methoxide in small portions. After 45 min, iodomethane was added dropwise. Stirring was continued for 2.5 days. The mixture was filtered through a 1.5-in silica gel pad, rinsing with large excess volume of ethyl acetate. The combined filtrate and rinsing were concentrated to a dark yellow oil, which was purified by flash column chromatography, eluting with hexanes, CH₂Cl₂, and CH₂Cl₂-MeOH (50:1). Removal of solvents afforded 5.10 g (81%) of *N, N'*-dimethyl 1-methyl-5-nitro-3-pyrazole amide as a solid (MH⁺ = 199.0), contaminated by ~13% of 2-methylated isomer.

Step C

A solution of *N, N'*-dimethyl 1-methyl-5-nitro-3-pyrazolecarboxamide (5.10 g, 25.29 mmol), obtained from step B, in 250 mL of ethanol was degassed via house vacuum, and then refilled with nitrogen. Solid palladium (10% on activated carbon, wet with <50% water, 2.5 g) was added, the black suspension was degassed via house vacuum and then refilled with hydrogen gas supplied by a gas balloon. The

mixture was stirred at room temperature under a hydrogen atmosphere for 4 h, and filtered through a Celite pad, which was rinsed with ethanol. The filtrate and rinsing were combined, concentrated under reduced pressure to give 4.17 g (98%) of the amino-pyrazole product as a solid ($MH^+ = 169.0$).

5

Step D

To a stirred solution of amino-pyrazole (1.0 g, 5.95 mmol), prepared in step C, in 40 mL of CH_2Cl_2 at room temperature was added benzyl chloroformate (2.7 mL, 17.97 mmol). Solid potassium carbonate (4.1 g, 29.71 mmol) was added in one portion. After 24 h, methanol (5 mL) was added to the mixture, and stirring was continued for additional 2 h. Insoluble material was removed by filtration, and washed with methanol. The combined filtrate and rinsing were concentrated under reduced pressure to a thick syrup, which was separated by preparative TLC (CH_2Cl_2 -MeOH = 30:1). The silica was extracted with MeOH and CH_2Cl_2 , the extracts were filtered and concentrated under reduced pressure to yield 1.16 g (64%) of the pyrazole benzyl carbamate as a solid ($MH^+ = 303.1$).

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Step E

To a stirred solution of pyrazole benzyl carbamate (1.0 g, 3.31 mmol), obtained from step D, in 100 mL of toluene at room temperature was added "Clayfen" (see note below) (3.5 g) in one portion. The dark purplish suspension was heated to 70 °C and continued at 70-80 °C for 2.5 d. After cooled to room temperature, the mixture was filtered through a thin Celite pad. The solid residue and the filtration pad were rinsed with CH_2Cl_2 , and filtered. The combined filtrates were concentrated to a yellowish oil, which was purified by preparative TLC (CH_2Cl_2 -MeOH = 20:1). The silica was extracted with CH_2Cl_2 and methanol, the extracts were filtered and concentrated under reduced pressure to give 0.822 g (72%) of the nitro-pyrazole benzyl carbamate as a yellowish oil ($MH^+ = 348.1$). Note: "Clayfen", clay-supported Iron (III) nitrate, was prepared according to literature procedures, see: Cornelis, A.; Laszlo, P. *Synthesis*, 1980, 849. To a stirred acetone solution (30 mL) at room temperature was added solid $Fe(NO_3)_3 \cdot 9H_2O$ (1.8 g) in small portions. After 5 min, K-10 bentonite clay (2.4 g) was added. Stirring was continued for 30 min, and the resulting suspension was

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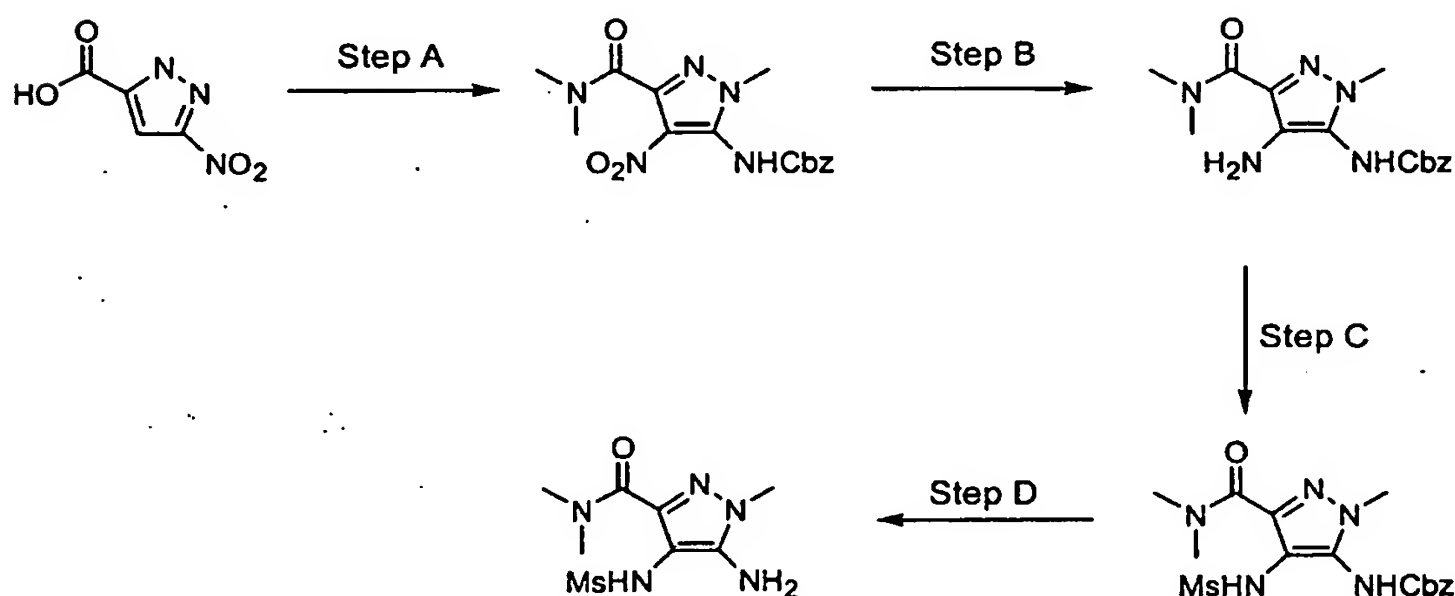
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concentrated under reduced pressure (water bath temperature $\leq 30^{\circ}\text{C}$). The freshly prepared material was used right away in the reaction above.

Step F

- 5 A solution of nitro-pyrazole benzyl carbamate (410.0 g, 1.18 mmol), available from step E, in 20 mL of ethanol was degassed via house vacuum, and refilled with nitrogen. Solid palladium (10% on activated carbon, wet with $<50\%$ H_2O , 280.0mg) was added. The black suspension was degassed via house vacuum, and refilled with hydrogen gas supplied by a gas balloon. The mixture was stirred for 20 h
- 10 under a hydrogen atmosphere, and filtered through a 1-in Celite pad, rinsing with excess volume of methanol. The filtrate and rinsing were concentrated to a reddish oil, which was purified by preparative TLC ($\text{CH}_2\text{Cl}_2\text{-MeOH} = 15:1$). The silica was extracted with methanol, the extracts were filtered, and the filtrate was concentrated under reduced pressure to an oil, which solidified while being dried on high vacuum,
- 15 yielding 120.0 mg (56%) of diamino-pyrazole product ($\text{MH}^+ = 184.0$).

PREPARATIVE EXAMPLE 33



20 Step A

Nitro-pyrazole benzyl carbamate was prepared from 5-nitro-3-pyrazolecarboxylic acid according to the procedure described in Preparative Example 32.

Step B

To a solution of nitro-pyrazole benzyl carbamate (410.0 mg, 1.18 mmol), obtained from step A, in 17 mL of ethyl acetate at room temperature was added Tin (II) chloride dihydrate (1.33 g, 5.90 mmol) in one portion. The mixture was heated to 80 °C and continued for 2 h. After cooled to room temperature, a saturated NaHCO₃ aqueous solution was added dropwise to the mixture until pH approximately 7. An additional volume of ethyl acetate (20 mL) was added, the mixture was stirred overnight, and filtered through a 1-in Celite pad. The two layers of the filtrate were separated. The organic layer was washed with brine once. The aqueous washing was combined with the aqueous layer, and extracted with ethyl acetate once. The combined organic layers were dried with Na₂SO₄, filtered and concentrated, further dried on high vacuum, to afford 361.5 mg (97%) of amino-pyrazole benzyl carbamate as a solid (MH⁺ = 318.1).

Step C

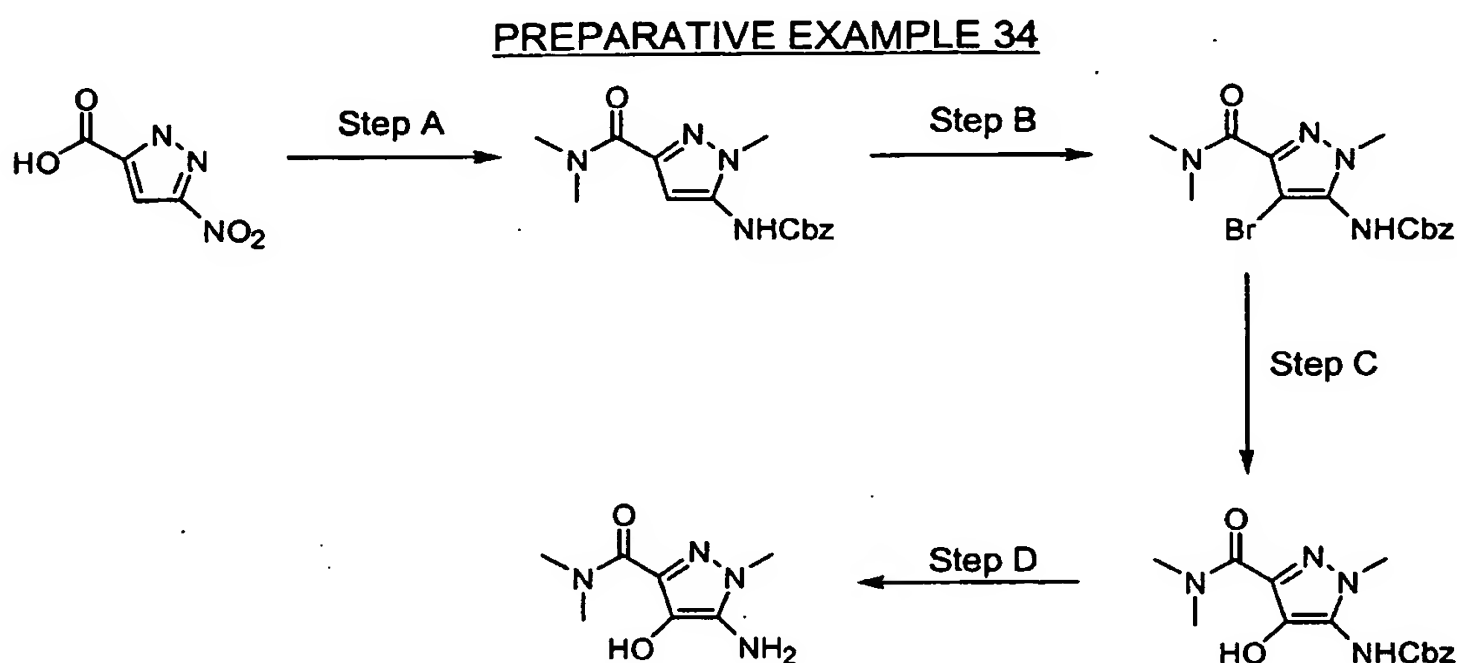
To a stirred solution of amino-pyrazole benzyl carbamate (180.0 mg, 0.57 mmol), prepared in step B, in 11 mL of CH₂Cl₂ at -78 °C was added triethylamine (0.32 mL, 2.30 mmol). A 1.0 M solution of methanesulfonyl chloride in CH₂Cl₂ (1.7 mL, 1.7 mmol) was added dropwise along the inside wall of the flask. The mixture was stirred for 2.5 h while the temperature of the cooling bath was increased slowly from -78 °C to -25 °C. A saturated NaHCO₃ aqueous solution (5 mL) was added to the mixture, and it was further diluted with 25 mL of CH₂Cl₂. The cooling bath was removed, stirring was continued for an additional 1.5 h, and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (30 mL), and the combined organic layers were washed with a saturated NaHCO₃ aqueous solution (30 mL) and brine (30 mL). The organic layer was dried by Na₂SO₄, and concentrated to an oil, which was purified by preparative TLC (CH₂Cl₂-MeOH = 20:1). The silica was extracted with CH₂Cl₂ and methanol, the extracts were filtered and concentrated to a colorless oil, solidified while being dried on high vacuum, yielding 185.7 mg (83%) of the pyrazole methylsulfonamide as a solid (MH⁺ = 396.1).

Step D

To a nitrogen flushed solution of pyrazole methylsulfonamide (275.0 mg,

0.70 mmol), from step C, in 10 mL of ethanol was added solid palladium (10% on activated carbon, wet with < 50% water, 550.0 mg). The suspension was degassed via house vacuum, then filled with hydrogen gas supplied by a gas balloon. The mixture was stirred for 3.5 h under a hydrogen atmosphere, and filtered through a layer of Celite. The solid residue and the filtration pad were rinsed with ethanol and ethyl acetate, the combined filtrate and rinsing were concentrated under reduced pressure to give 173.0 mg (95%) of amino-pyrazole methylsulfonamide as a solid ($MH^+ = 262.0$).

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Step A

Pyrazole benzyl carbamate was prepared from 5-nitro-3-pyrazolecarboxylic acid in 4 steps according to the procedure described in Preparative Example 32.

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Step B

To a solution of pyrazole benzyl carbamate (115.0 mg, 0.38 mmol), prepared in step A, in 6 mL of CH_2Cl_2 at room temperature was added solid potassium carbonate in one portion. A solution of bromine was added dropwise to the stirred mixture. After 6 h, 30 mL of H_2O was added, and the mixture was extracted with CH_2Cl_2 (30 mL x 3). The combined organic extracts were washed with a 10% $Na_2S_2O_3$ aqueous solution (20 mL), a saturated $NaHCO_3$ aqueous solution (20 mL) and brine (20 mL), and dried with Na_2SO_4 . Evaporation of solvent gave a slightly yellow oil, which was purified by preparative TLC (CH_2Cl_2 -MeOH = 20:1). The silica was extracted with CH_2Cl_2 and methanol, the extracts were filtered and

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concentrated under reduced pressure to afford an oil, which was further dried on high vacuum, yielding 134.2 mg (93%) of the bromo-pyrazole benzyl carbamate ($MH^+ = 381$).

5 Step C

If one were to treat the bromo-pyrazole benzyl carbamate compound from step B with *n*-butyl lithium followed by methyl borate, it would convert the bromo-pyrazole benzyl carbamate to the corresponding boronic ester. Subsequent one-pot oxidation of the boronic ester with H_2O_2 aqueous solution would afford the hydroxy-pyrazole benzyl carbamate.

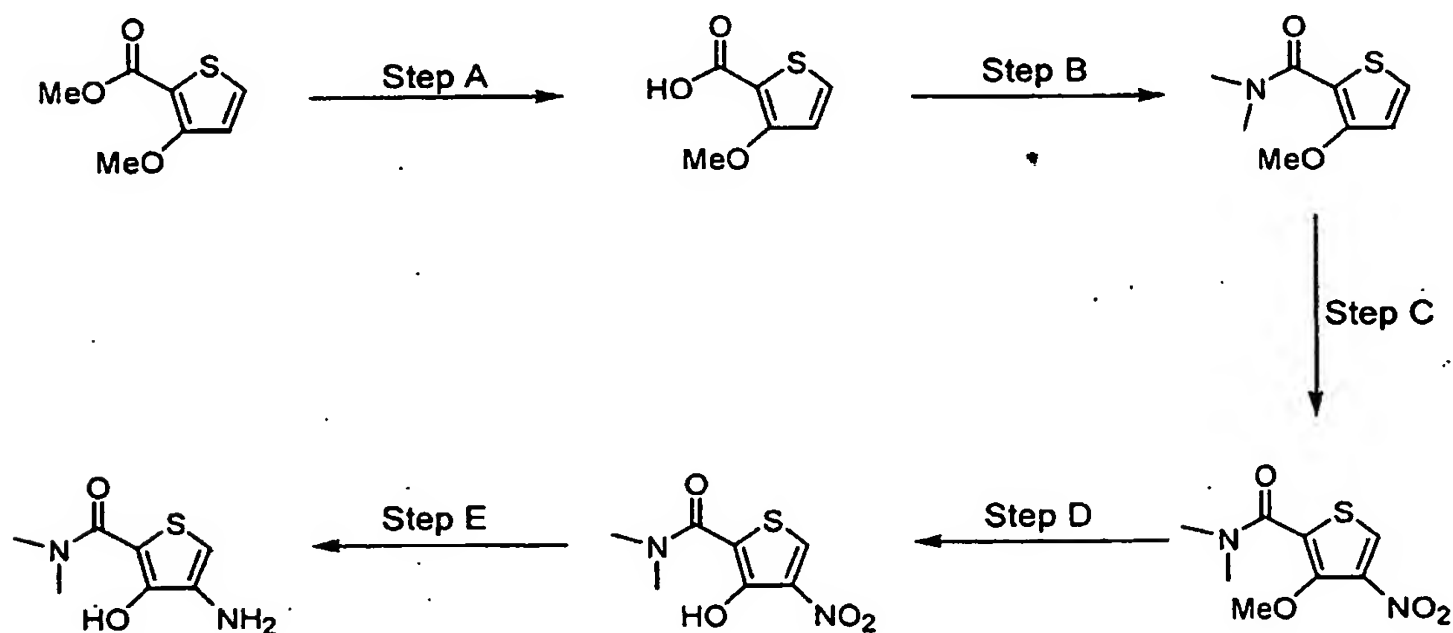
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Step D

Treatment of the hydroxy-pyrazole benzyl carbamate from step C with hydrogen under the conditions of palladium (10% on activated carbon) in ethanol would afford the desired amino-hydroxy pyrazole.

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PREPARATIVE EXAMPLE 35



Step A

To a solution of methyl 3-methoxythiophene carboxylate (2.0 g, 11.6 mmol) in 20 mL of THF at room temperature was added dropwise a 1.0 M sodium hydroxide aqueous solution (17.0 mL, 17.0 mmol). After addition, the mixture was heated to 75 °C (oil bath temperature) and continued for 18 h. The mixture was cooled to room temperature, treated with a 1.0 M hydrochloride aqueous solution until pH approximately being 2. The acidified mixture was extracted with 100 mL of

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CH₂Cl₂-CH₃CN (1:1, v/v), 50 mL of CH₂Cl₂, and 50 mL of CH₃CN. The combined organic extracts were washed with brine (30 mL), dried over Na₂SO₄, and concentrated under reduced pressure to a solid, which was further dried on high vacuum, yielding 1.84 g (100%) of 3-methoxythiophene carboxylic acid (MH⁺ = 159.0).

Step B

To a suspension of 3-methoxythiophene carboxylic acid (1.84 g, 11.61 mmol), from step A, in 60 mL of acetonitrile at room temperature was added bromotripyrroli-dinophosphonium hexafluorophosphate (PyBrop, 5.40 g, 11.60 mmol), dimethyl amine (2.0 M in THF, 14.5 ml, 29.0 mmol) and diisopropylethyl amine (5.0 mL, 28.63 mmol) successively. After stirred for 1.5 day, the mixture was concentrated under reduced pressure to a yellow oil, which was purified by preparative TLC (CH₂Cl₂-MeOH = 40:1). The silica was extracted with CH₂Cl₂ and methanol; the extracts were filtered and concentrated to an oil, which was further dried on high vacuum, yielding 4.16 g of *N, N*-dimethyl 3-methoxythiophene amide (contaminated by PyBrop impurity) (MH⁺ = 186.0).

Step C

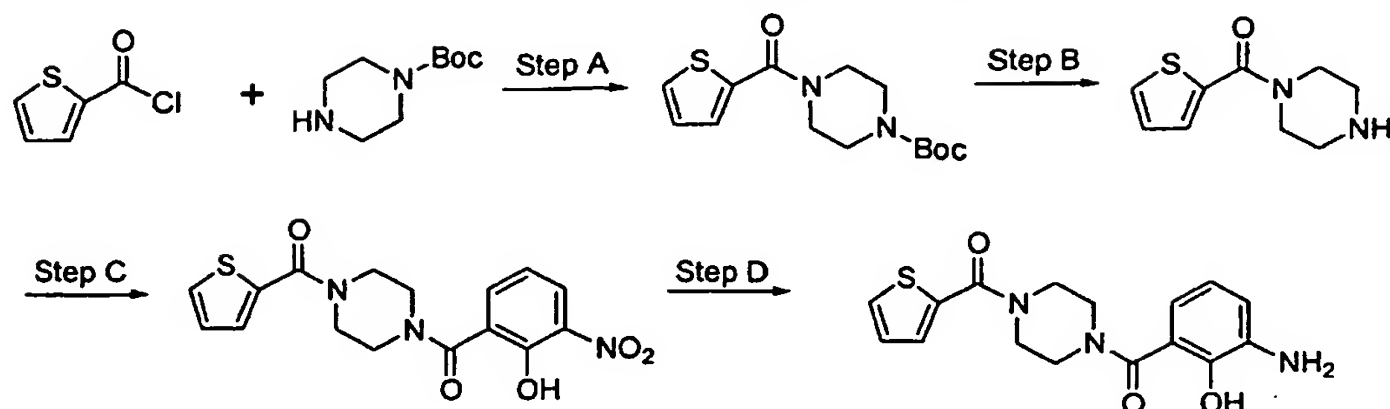
To a vigorously stirred solution of thiophene amide (4.16g, prepared in step B) in 6 mL of concentrated sulfuric acid at -10 °C was added dropwise fuming nitric acid (0.6 mL, 14.28 mmol). After 1.5 h, the mixture was poured into 80 mL of a mixture of 1.0 M NaOH aqueous solution and ice (1:1, v/v). An additional 40 mL of H₂O was used to facilitate the transfer. The yellow precipitates were collected by filtration, washed with H₂O twice, and dried on high vacuum, to give 1.67 g of the nitro-thiophene product. The aqueous filtrates were extracted with CH₂Cl₂ (50 mL x 3). The extracts were washed with a sat. NaHCO₃ aqueous solution (30 mL) and brine (30 mL), and dried with Na₂SO₄. Evaporation of solvent afforded a yellow oil, which was purified by preparative TLC (CH₂Cl₂-MeOH = 50:1) to give an additional 0.144 g of the nitro-thiophene as a solid (1.81 g total, 68% over two steps, MH⁺ = 231.0).

Step D

To a vigorously stirred solution of methoxy-nitro-thiophene (900.0 mg, 3.91 mmol), obtained from step C, in 55 mL of anhydrous CH_2Cl_2 at -78°C was added dropwise along the inside wall of the flask a 1.0 M solution of boron tribromide in CH_2Cl_2 during a 15 min period. The mixture was stirred for 4 h while the temperature of the cooling bath was increased slowly from -78°C to -10°C , and poured into 100 mL of a mixture of ice and H_2O (~ 1:1, v/v). Additional 30 mL of H_2O and 30 mL of CH_2Cl_2 were used to rinse the flask. The combined mixture was stirred at room temperature over night, the two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL x 3). The organic layers were combined, washed with a sat. NaHCO_3 aqueous solution (50 mL x 2) and brine (50 mL x 2), dried with Na_2SO_4 , and concentrated to a yellow solid. The crude product was purified by flash column chromatography, eluting with hexanes, CH_2Cl_2 -hexanes (1:1 and 2:1). Removal of solvents afforded a solid, which was further dried on high vacuum, giving 615.2 mg (73%) of the hydroxy-nitro-thiophene amide ($\text{MH}^+ = 217.0$).

Step E

To a nitrogen flushed solution of hydroxy-nitro-thiophene amide (610.0 mg, 2.82 mmol), prepared in step D, in 60 mL of ethanol was added palladium hydroxide (20 wt% on activated carbon, wet with $\leq 50\%$ water, 610.0 mg). The suspension was degassed via house vacuum and refilled with hydrogen gas from a gas balloon. The mixture was first stirred at room temperature under a hydrogen atmosphere for 2 h, then heated to $70 - 80^\circ\text{C}$ and continued for 20 h. Solid material was removed by filtration through a 1-in Celite pad, the filtration pad was washed with 100 mL of ethanol, and the combined filtrates were concentrated to a light yellow solid. The crude product was treated with a mixture of CH_2Cl_2 -MeOH (~1:1, v/v), off-white solids precipitated out and collected by filtration as the first crop of the product (75.4 mg). The filtrate was concentrated to a solid residue, which was purified by flash column chromatography, eluting with CH_2Cl_2 -EtOH (10:1 and 2:1). Removal of solvents afforded 226.8 mg of the amino-hydroxy-thiophene amide as a solid (302.2 mg total, 58%, $\text{MH}^+ = 187.0$).

91
PREPARATIVE EXAMPLE 36Step A

2-Thiophenecarbonyl chloride (2.0mL, 18.7mmol) was dissolved in 100mL dichloromethane. After addition of diisopropylethylamine (4.1mL, 23.4mmol) and Boc-piperazine (3.66g, 19.7mmol), the mixture was stirred for 4h at room temperature. The resulting cloudy mixture was put into water (500mL) and acidified with 3N HCl to pH~1. Extraction with dichloromethane (2x100mL) and drying over sodium sulfate resulted in sufficiently pure product that was used in the next step without any further purification.

^1H NMR (300MHz, d_6 -DMSO) 1.60 (s, 9H), 3.29 (dd, 4H), 3.69 (dd, 4H), 7.23 (dd, 1H), 7.49 (d, 1H), 7.79 (d, 1H).

Step B

The crude material from Step A was dissolved in trifluoroacetic acid/dichloromethane (75mL, 4/1). After stirring for 2h, the reaction mixture was put into 1N sodium hydroxide (400mL). Extraction with dichloromethane (2x100mL) and drying over sodium sulfate resulted in sufficiently pure product that was used in Step C without any further purification.

^1H NMR (300MHz, d_6 -DMSO) 2.81 (dd, 4H), 3.63 (dd, 4H), 7.21 (dd, 1H), 7.46 (d, 1H), 7.82 (d, 1H).

Step C

The crude material (3.50g, 17.8mmol) from Step B was dissolved in dichloromethane (100mL). After addition of diisopropylethylamine (18.7mL, 107mmol), 3-nitrosalicylic acid (3.3g, 18.0mmol), and PyBrOP (10.4g, 22.3mmol), the resulting yellow mixture was stirred over night at room temperature before being put into 1N sodium hydroxide (200mL). Extraction with dichloromethane (2x200mL)

removed all PyBrOP by-products. The aqueous phase was acidified with 3N HCl and subsequently extracted with dichloromethane (3x 100mL). The combined organic phases of the acidic extraction were dried over sodium sulfate, concentrated, and finally purified by column chromatography

(dichloromethane/methanol = 10/1) to yield the desired product (2.31g, 34 % over 3 steps).

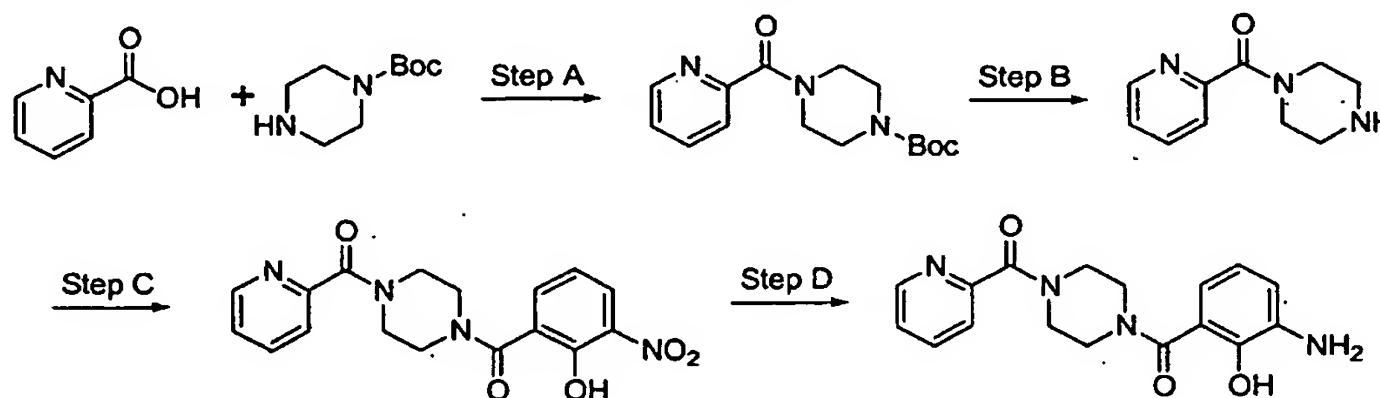
^1H NMR (300MHz, d_6 -DMSO) 3.30-3.90 (m, 8H), 7.10-8.20 (m, double signals due to E/Z-isomers, 6H), 10.82 (s, 1H).

Step D

The nitro-compound (2.3g, 6.4mmol) from Step C was dissolved in methanol (50mL) and stirred with 10% Pd/C under a hydrogen gas atmosphere over night. The reaction mixture was filtered through Celite and washed thoroughly with methanol. Finally, the filtrate was concentrated in vacuo and purified by column chromatography (dichloromethane/methanol = 10/1) to yield the desired product (1.78g, 84%).

^1H NMR (300MHz, d_6 -DMSO) 3.30-3.90 (m, 8H), 7.22 (m, 2H), 7.55 (d, 1H), 7.71 (d, 1H), 7.88 (d, 1H), 8.15 (d, 1H), 10.85 (bs, 1H).

PREPARATIVE EXAMPLE 37



Step A

Picolinic acid (3.0g, 24.3mmol) was suspended in SOCl_2 (15mL). After addition of dimethylformamide (5 drops), the reaction mixture was stirred for 4 hours. During this period the color changed from white to green to brown to finally dark wine-red and all solid went into solution. Evaporation of the solvent yielded the corresponding acid chloride as HCl-salt. Without any further purification, the solid was suspended in 120mL dichloromethane. After addition of diisopropylethylamine

(12.7mL, 73mmol) and Boc-piparazine (4.8g, 25.5mmol), the reaction was stirred over night at room temperature. The resulting cloudy mixture was put into water (500mL) and extracted with dichloromethane (2x100mL). Drying over sodium sulfate resulted in sufficiently pure product that was used in Step B without any further purification.

¹H NMR (300MHz, d₆-DMSO) 1.63 (s, 9H), 3.21 (dd, 4H), 3.61 (dd, 4H), 7.57 (dd, 1H), 7.63 (d, 1H), 7.98 (dd, 1H), 8.70 (d, 1H).

Step B

The crude material from Step A was dissolved in trifluoroacetic acid/dichloromethane (75mL, 4/1). After stirring for 2days, the reaction mixture was put into 1N sodium hydroxide (400mL). Extraction with dichloromethane (2x100mL) and drying over sodium sulfate resulted in sufficiently pure product that was used in Step C without any further purification.

¹H NMR (300MHz, d₆-DMSO) 2.77 (dd, 2H), 2.83 (dd, 1H), 3.38 (dd, 2H), 3.64 (dd, 1H), 7.58 (dd, 1H), 7.62 (d, 1H), 8.00 (dd, 1H), 8.67 (d, 1H).

Step C

The crude material (1.35g, 7.06mmol) from Step B was dissolved in dichloromethane (50mL). After addition of diisopropylethylamine (3.7mL, 21.2mmol), 3-nitrosalicylic acid (1.36g, 7.41mmol), and PyBrOP (3.62g, 7.77mmol), the resulting yellow mixture was stirred over night at room temperature before being put into 1N sodium hydroxide (300mL). Extraction with dichloromethane (2x100mL) removed any PyBrOP products. The aqueous phase was acidified with 3N HCl.

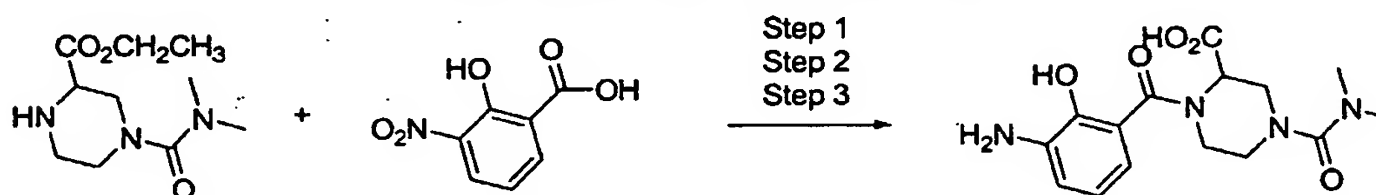
Careful adjustment of the pH with saturated sodium carbonate solution to almost neutral crushed the desired compound out of solution. The aqueous phase was subsequently extracted with dichloromethane (3x 100mL). The combined organic layers of the neutral extraction were dried over sodium sulfate, concentrated, and finally purified by column chromatography (dichloromethane/methanol = 20/1) to yield the desired product (1.35g, 16% over 3 steps).

¹H NMR (300MHz, d₆-DMSO) 3.30-3.95 (m, 8H), 7.22 (m, 1H), 7.61 (m, 1H), 7.73 (d, 2H), 8.03 (m, 1H), 8.17 (m, 1H), 8.69 (m, 1H), 10.82 (s, 1H).

Step D

The nitro-compound (1.35g, 3.79mmol) from Step C was dissolved in methanol (60mL) and stirred with 10% Pd/C under a hydrogen gas atmosphere over night. The reaction mixture was filtered through Celite and washed thoroughly with methanol. Finally, the filtrate was concentrated in vacuo and purified by column chromatography (dichloromethane/methanol = 20/1) to yield the desired product (1.10g, 89 %).

¹H NMR (300MHz, d₆-DMSO) 3.50-3.85 (m, 8H), 6.47 (dd 1H), 6.74 (m, 2H), 7.59 (dd, 1H), 7.71 (d, 1H), 8.04 (dd, 1H), 8.68 (d, 1H).

PREPARATIVE EXAMPLE 38Step 1

3-Nitrosalicylic acid (3.61g, 0.0197g), DCC (2.03g, 0.0099mol) and ethyl acetate (130mL) were combined in a round bottom flask and stirred for 15min. 4-Dimethylcarbamoyl-piperazine-2-carboxylic acid ethyl ester (4.51g, 0.0197g) was added, and the reaction was stirred for 72 hours. The reaction mixture was concentrated then dissolved in dichloromethane. The organic phase was washed once with 0.1N sodium hydroxide. The aqueous phase was back extracted once with dichloromethane. The aqueous phase was acidified and wash three times with ethyl acetate. The aqueous phase was concentrated and purified by column chromatography (5% methanol/DCM).

MS: calculated: 394.15, found:395.0

¹H NMR (300 MHz, CDCl₃) 1.32 (t, 3H), 2.86 (m, 7H), 3.15 (m, 1H), 3.51 (m, 4H), 4.24 (m, 3H), 7.15 (m, 1H), 7.66 (m, 1H), 8.20 (m, 1H), 10.86 (bs, 1H).

Step 2

4-Dimethylcarbamoyl-1-(2-hydroxy-3-nitro-benzoyl)-piperazine-2-carboxylic acid ethyl ester (0.80g, 0.002mol) and methanol (50mL) were combined in a round bottom flask. The system was purged with argon. To the solution was added 5% palladium on carbon (~100mg). The flask was purged with hydrogen and stirred

overnight. The reaction was filtered through a pad of celite and washed with methanol. The material was concentrated then purified by column chromatography (6% methanol/DCM). Isolated product (0.74g, 0.002mol, 100%).

MS: calculated: 364.17, found:365.1

5 ^1H NMR (300 MHz, CDCl_3) 1.27 (t, 3H), 2.85 (m, 8H), 3.18 (1H), 3.45 (m, 3H), 4.19 (m, 3H), 3.90 (m, 3H)

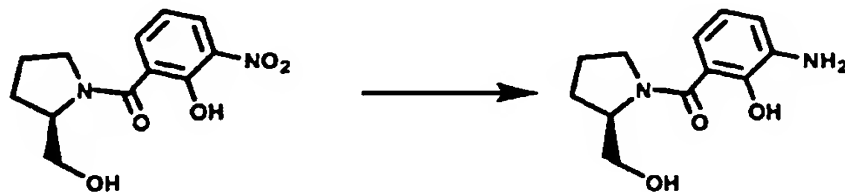
Step 3

10 1-(3-Amino-2-hydroxy-benzoyl)-4-dimethylcarbamoyl-piperazine-2-carboxylic acid ethyl ester (0.74g, 0.002mol) was suspended in a solution of dioxane (10mL) and water (10mL). Lithium hydroxide (0.26g, 0.0061mol) was added and the mixture stirred for two hours. The solution was acidified to pH=6 with 3N HCl then extracted with butanol. The extracts were combined, dried over sodium sulfate and concentrated.

15 MS: calculated: 336.14, found:337.1

^1H NMR (300 MHz, CD_3OD) 2.86 (m, 7H), 3.23 (m, 3H), 3.54 (m, 3H), 6.92 (m, 2H), 7.23 (m, 1H).

PREPARATIVE EXAMPLE 39

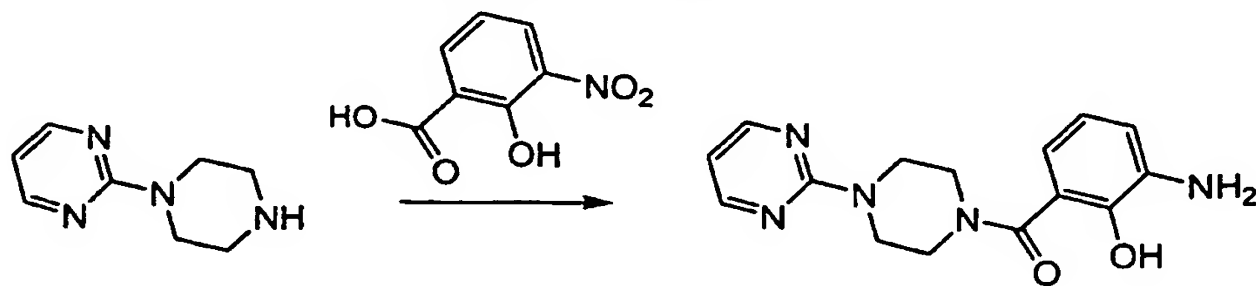


20

The product from Preparative Example 1 was stirred with 10% Pd/C under a hydrogen gas atmosphere overnight. The reaction mixture was filtered through celite, the filtrate concentrated *in vacuo*, and the resulting residue purified by column chromatography (silica gel, 4% MeOH/ CH_2Cl_2 saturated with NH_4OH) to give the product (129mg, 43%, $\text{MH}^+=237$).

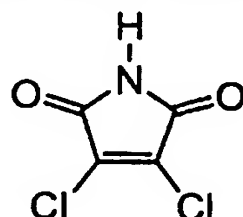
25

PREPARATIVE EXAMPLE 39.1



In essentially the same manner as was described in Preparative Example 39, the amine product above was obtained (50% yield, $MH^+ = 300.1$).

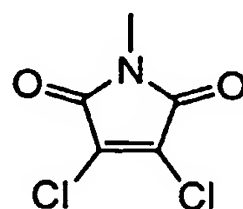
PREPARATIVE EXAMPLE 40



5

The compound above is prepared according to the literature procedure Am. Chem. J.; 18; 1896; 334.

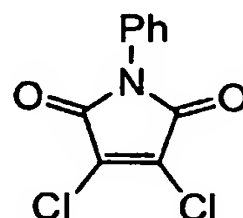
PREPARATIVE EXAMPLE 41



10

The compound above is commercially available from Maybridge Chemical Co.

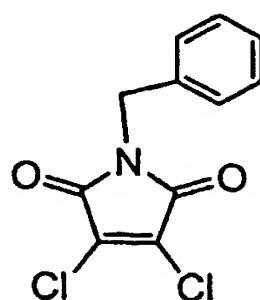
PREPARATIVE EXAMPLE 42



15

The compound above is commercially available from Salor Chemical Co.

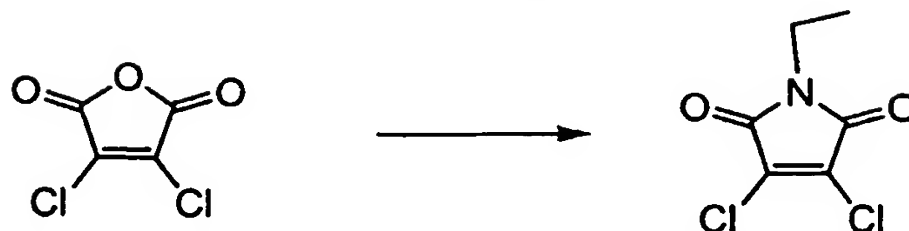
PREPARATIVE EXAMPLE 43



The compound above is commercially available from Maybridge Chemical Co.

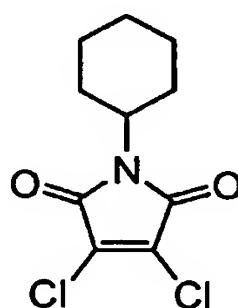
20

97
PREPARATIVE EXAMPLE 44



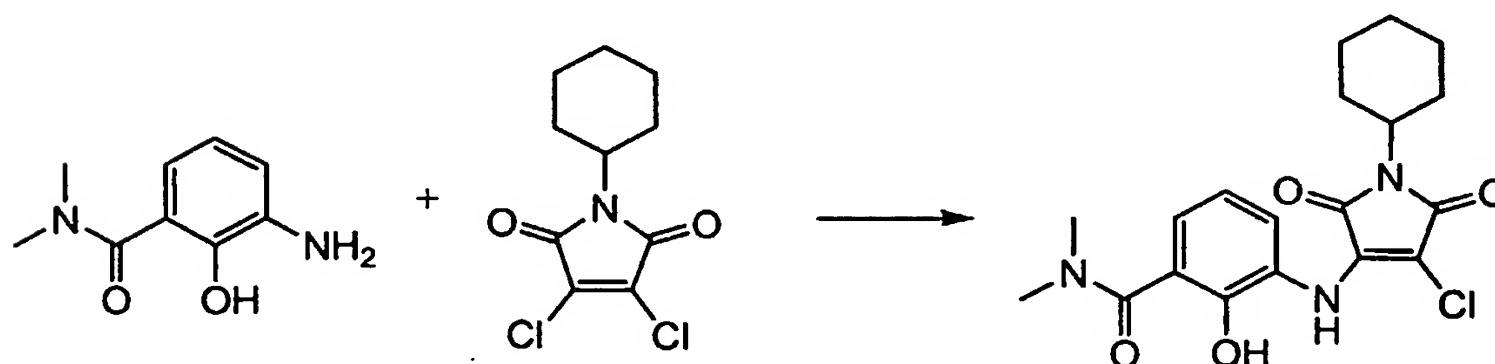
If one were to follow the procedure described in Bioorg. Med. Chem.; 7; 6; 1999; 1067-1074 but using ethyl amine instead of methyl amine, one could obtain the product above.

PREPARATIVE EXAMPLE 45



The compound above is prepared according to the literature procedure Chem. Heterocycl. Compd. 1992, 28, 331-335.

PREPARATIVE EXAMPLE 50



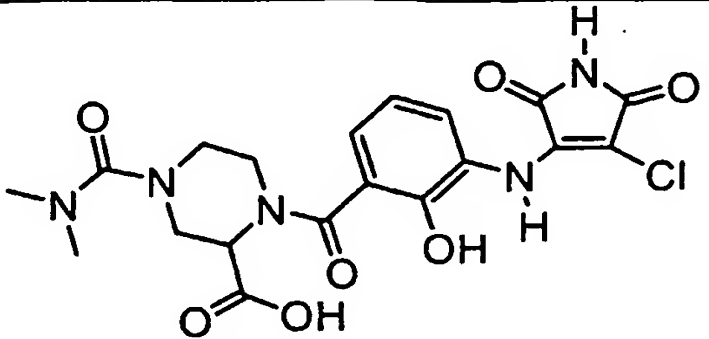
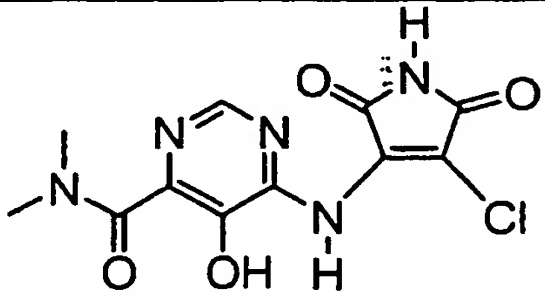
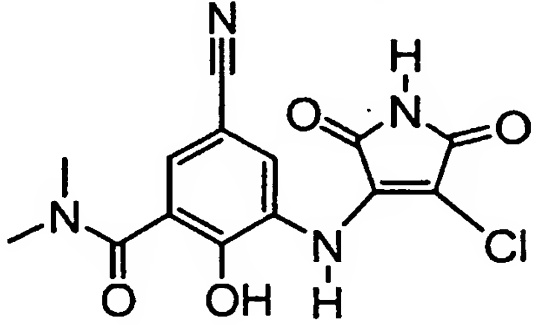
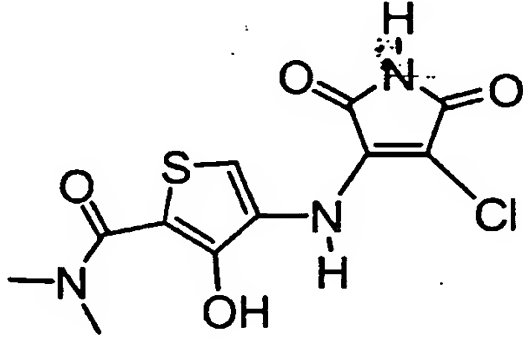
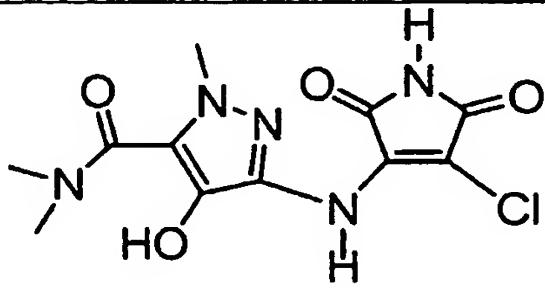
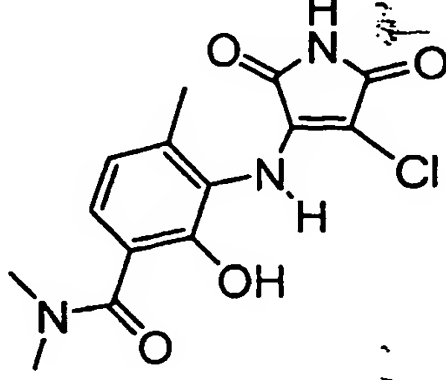
If one were to follow the procedure outlined in the literature: Chem. Heterocycl. Compd. 1992, 28, 331-335, but using the product from Preparative Example 3 instead of pyrrolidine, then one would obtain the product above.

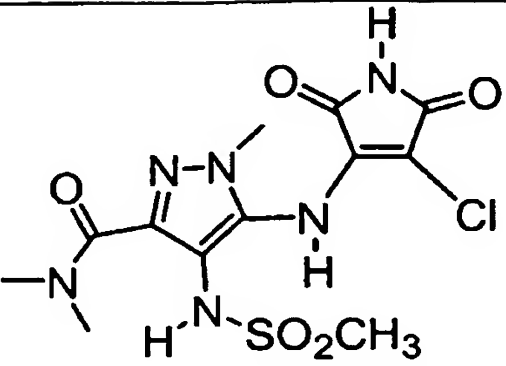
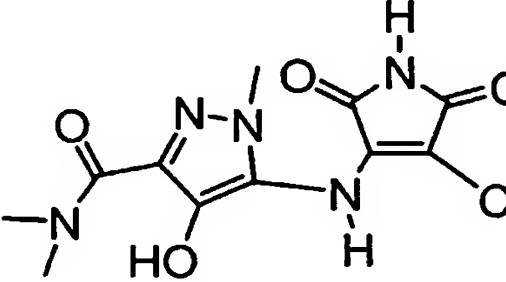
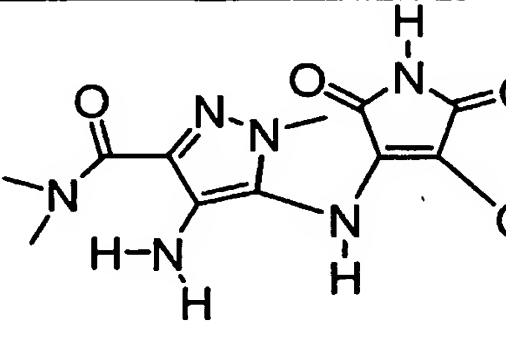
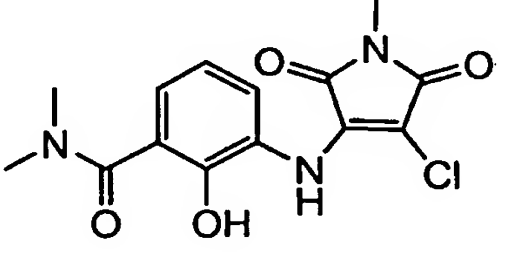
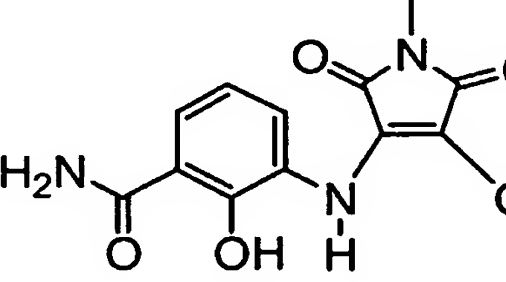
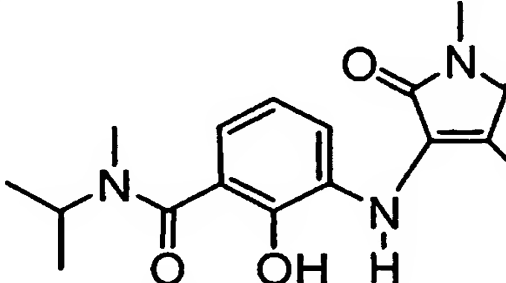
PREPARATIVE EXAMPLE 51-112

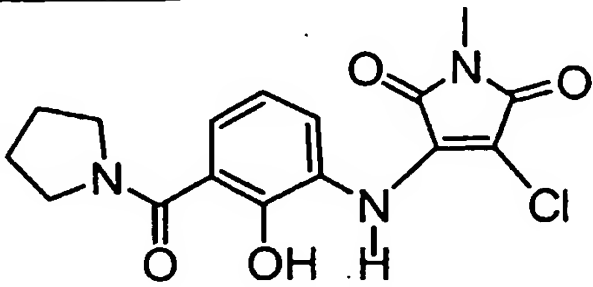
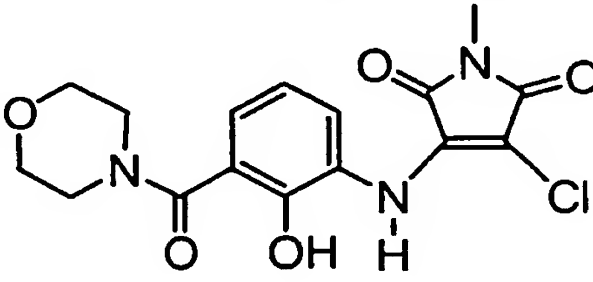
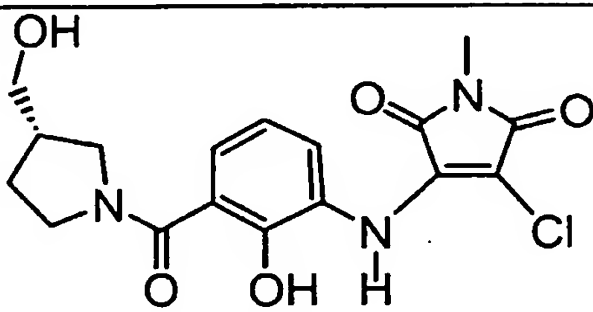
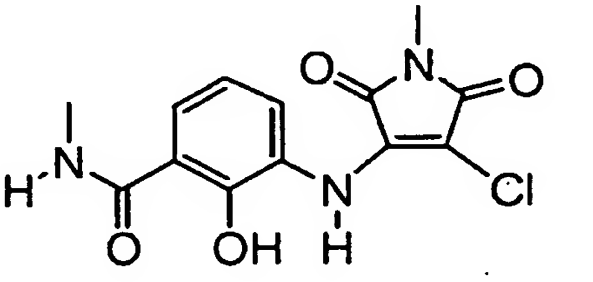
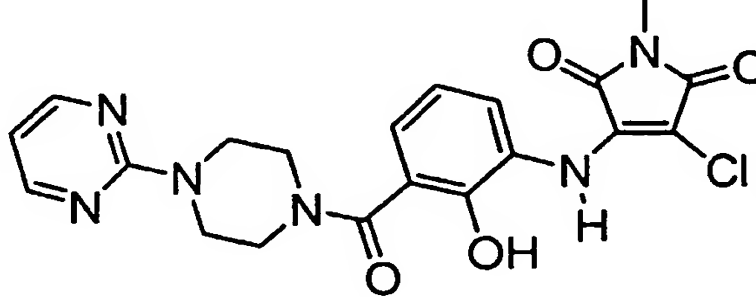
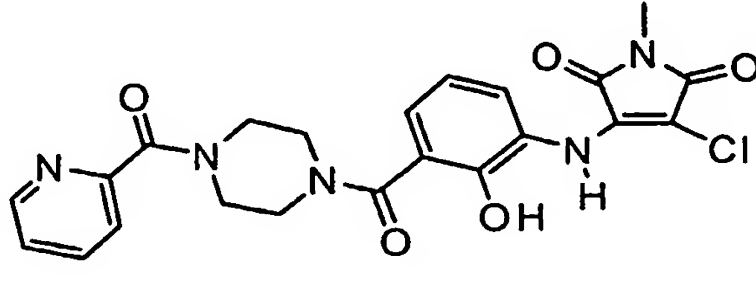
Following the procedure set forth in Preparative Example 50 but using the amine from the Preparative Example indicated and the appropriate dichloro

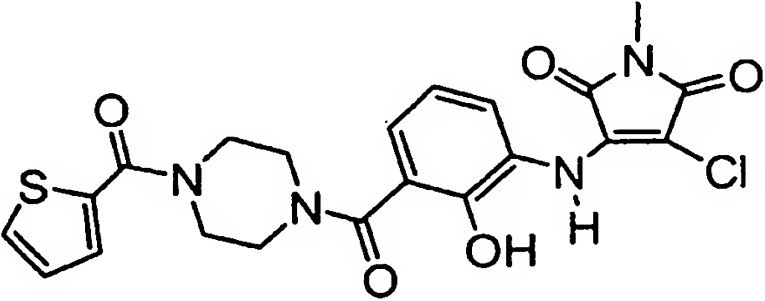
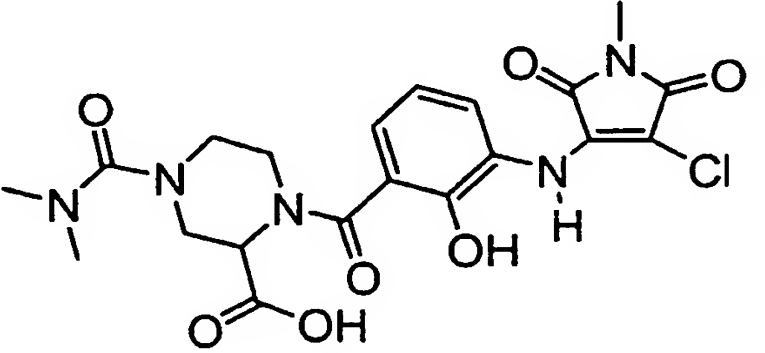
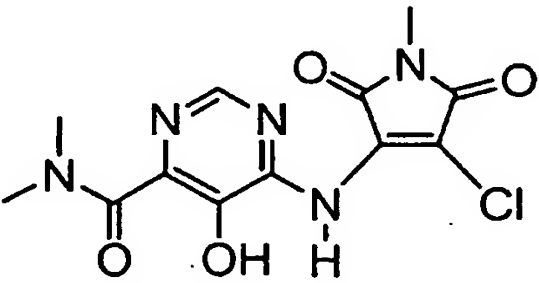
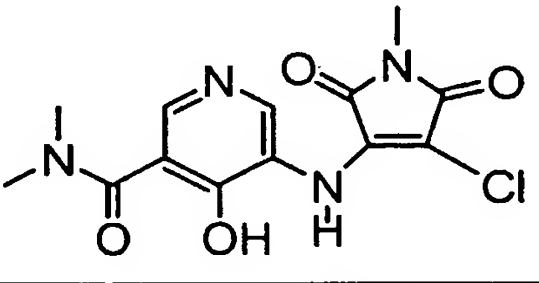
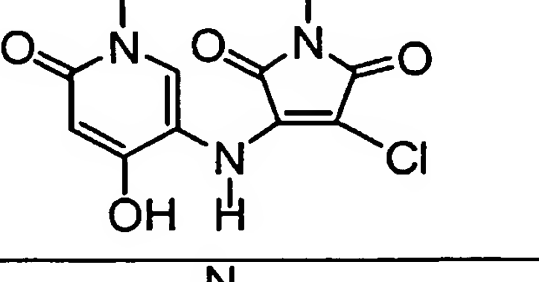
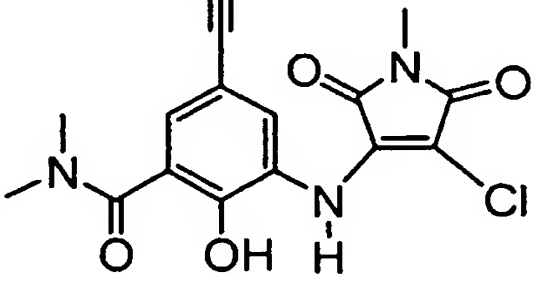
compound from the Preparative Example indicated, the chloro intermediate products listed in the table below would be obtained.

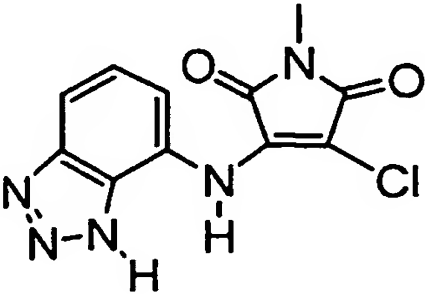
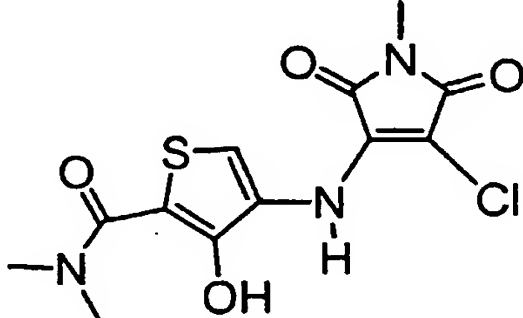
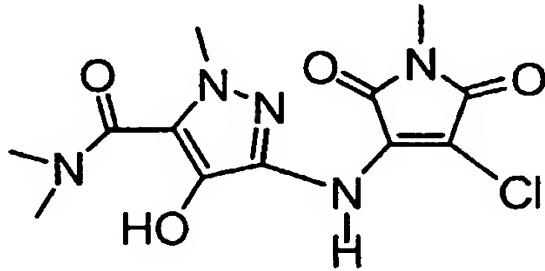
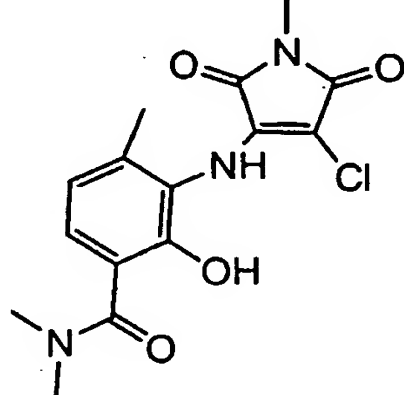
Prep Ex.	Prep Ex of Amine	Prep Ex of Dichloro	Product
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52	6	40	
53	8	40	
54	7	40	
55	37	40	

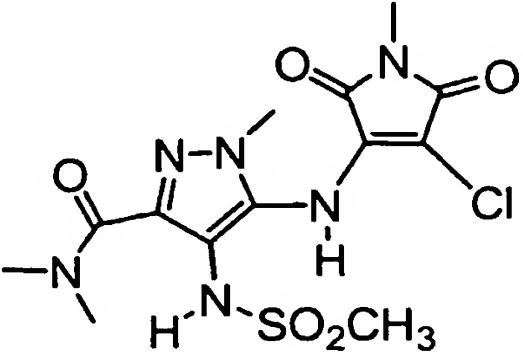
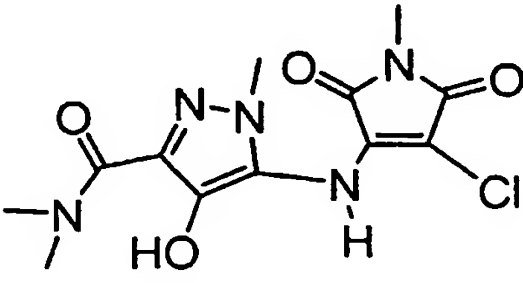
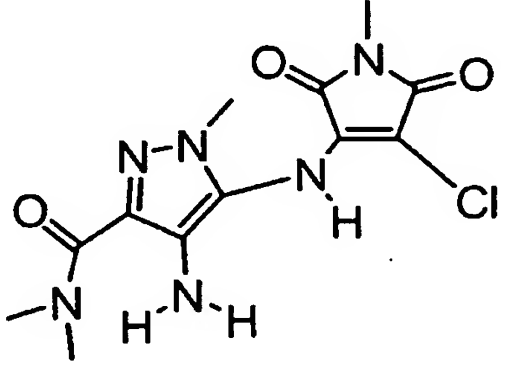
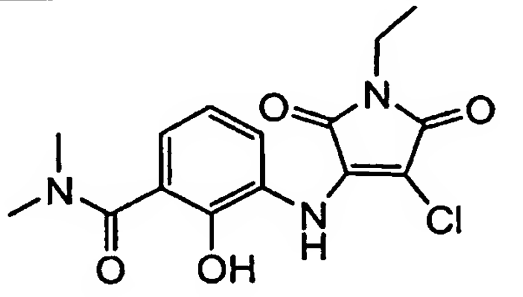
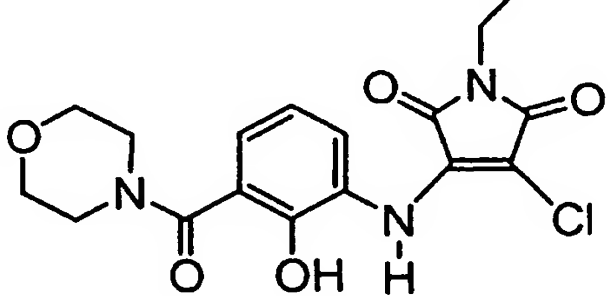
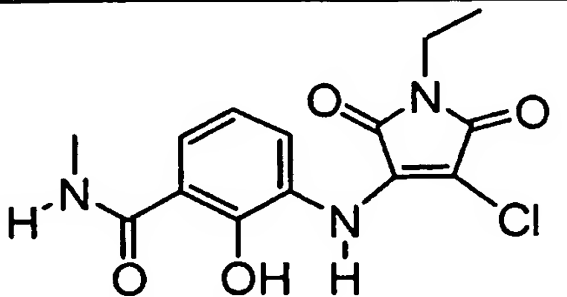
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57	29	40	
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59	35	40	
61	28	40	
63	26	40	

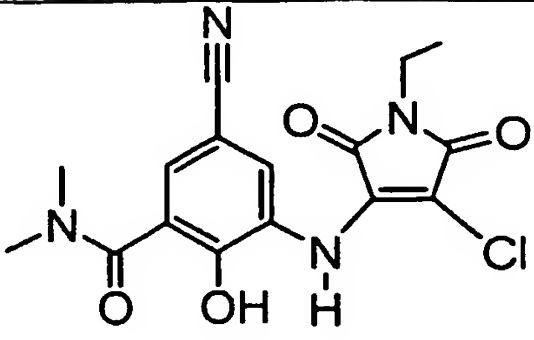
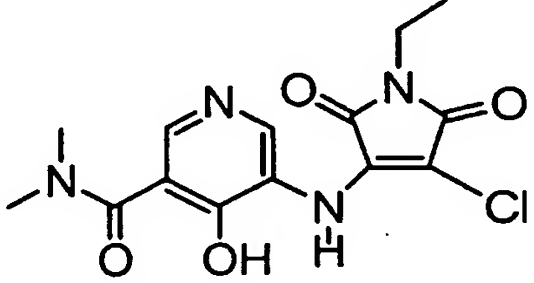
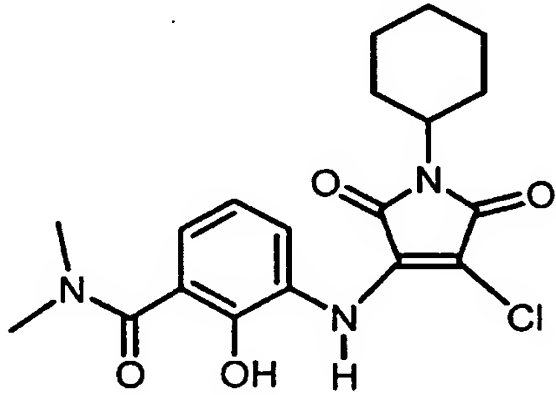
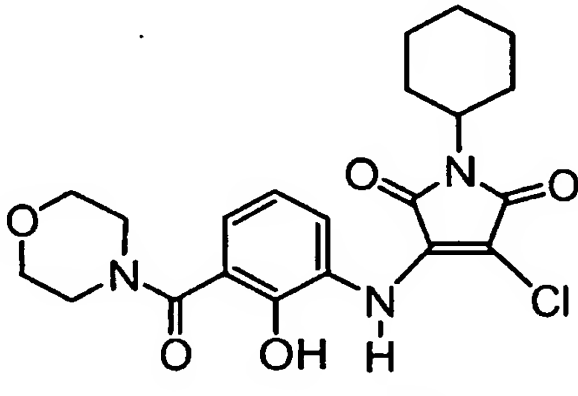
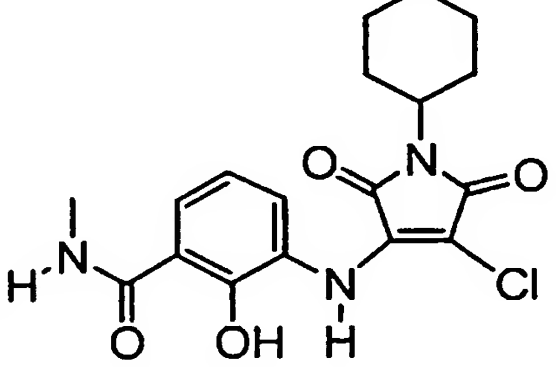
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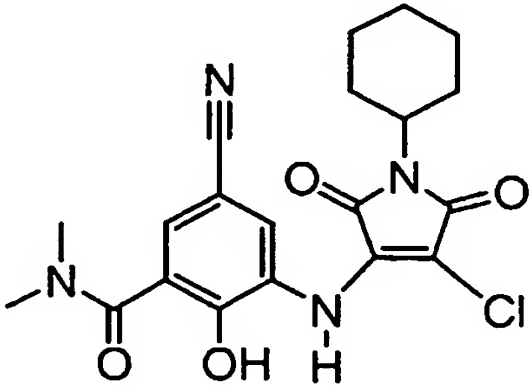
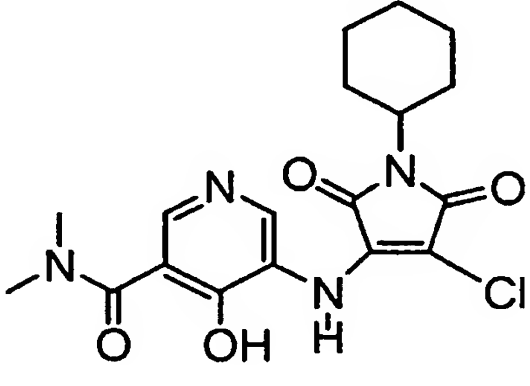
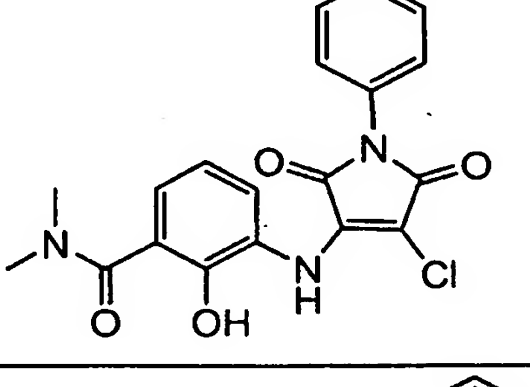
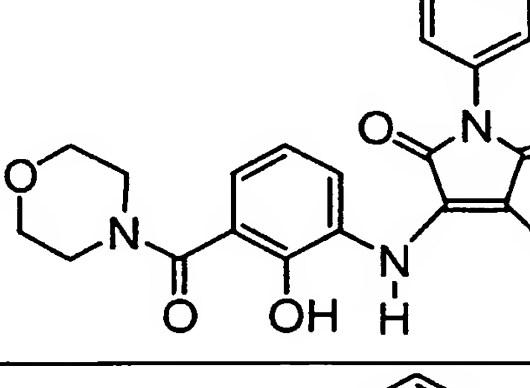
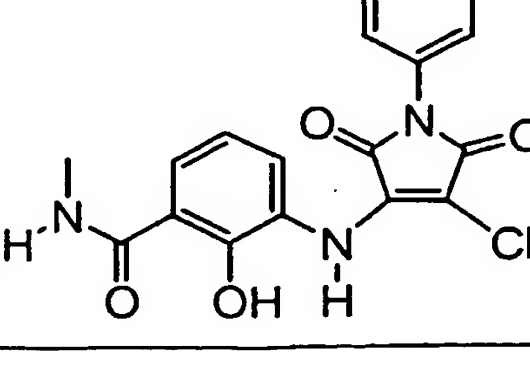
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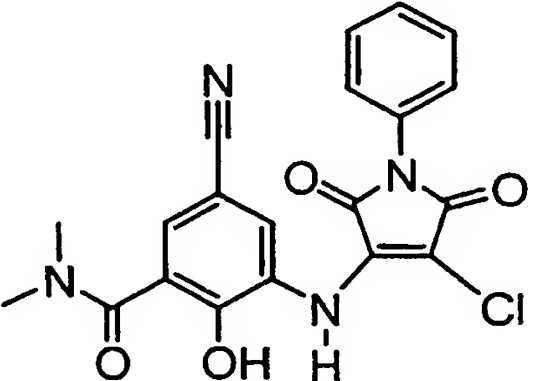
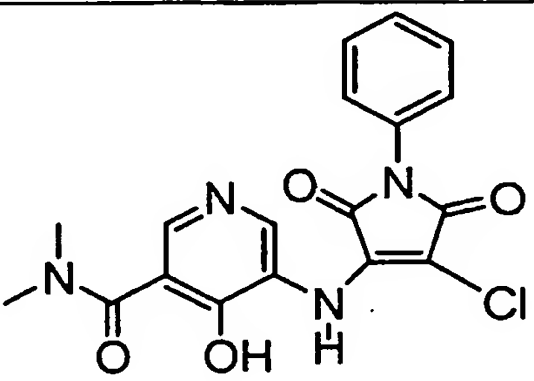
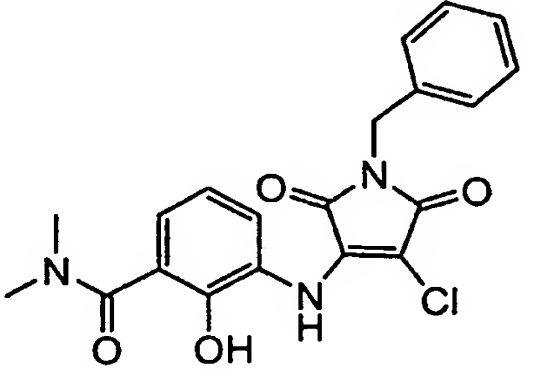
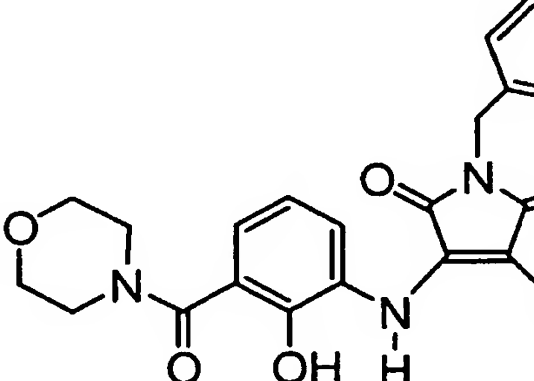
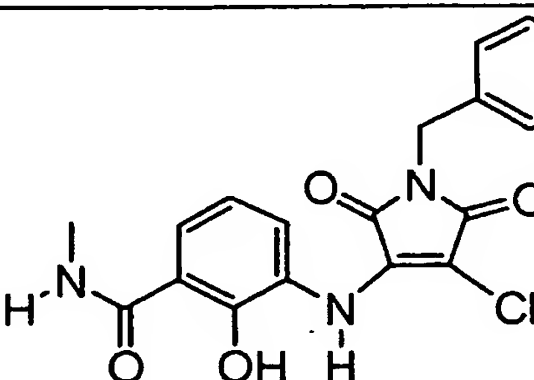
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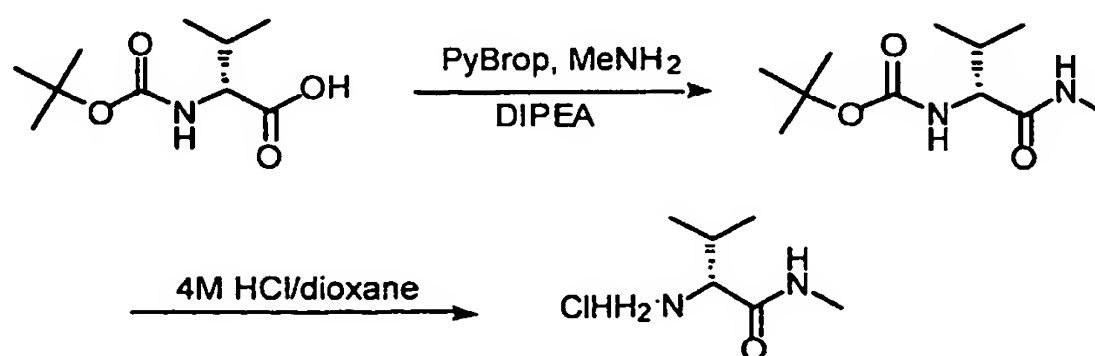
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102	8	42	
103	7	42	

104	25	42	
105	30	42	
106	3	43	
107	8	43	
108	7	43	

109	25	43	
110	30	43	
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112	30	40	

PREPARATIVE EXAMPLE 120



Step A

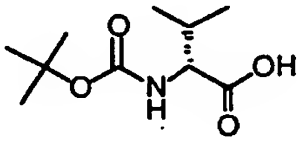
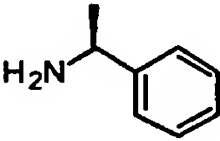
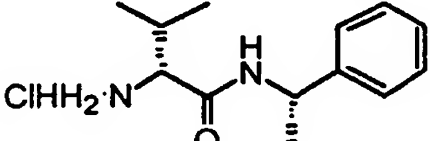
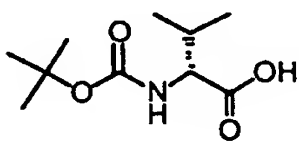
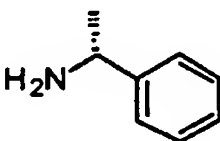
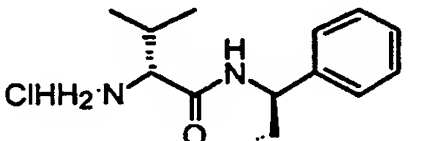
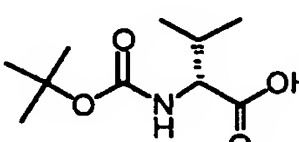
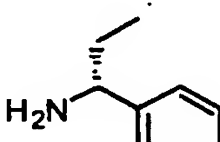
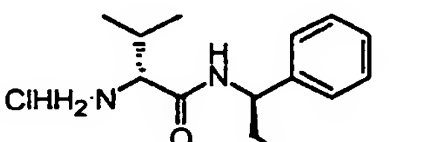
To a solution of N-protected amino acid (1.5 g, 6.9 mmol) in CH₂Cl₂ (25 mL) at room temperature was added DIPEA (3.6 mL, 20.7 mmol), and (PyBrop) (3.4 g, 6.9 mmol) followed by MeNH₂ (6.9 mL, 13.8 mmol, 2.0 M in CH₂Cl₂). The resulting solution was stirred for 18h at room temperature (until TLC analysis deemed the reaction to be complete). The resulting mixture was washed sequentially with 10% citric acid (3 x 20 mL), sat. aq. NaHCO₃ (3 x 20 mL), and brine (3 x 20 mL). The organic layer was dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with CH₂Cl₂/MeOH (40:1) to afford 1.0 g (63% yield) of a white solid.

Step B

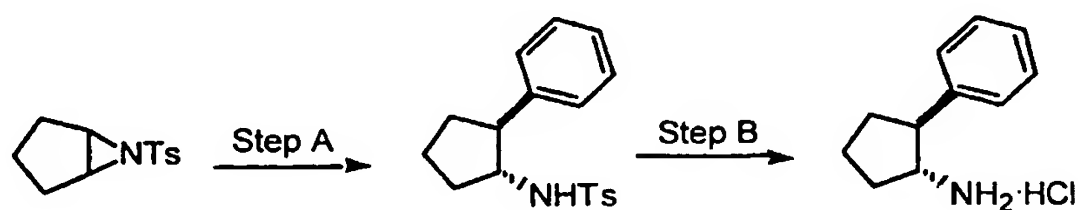
To a round bottom flask charged with the N-protected amide (1.0 g, 4.35 mmol) from Step A above, was added 4N HCl/dioxane (10 mL). The mixture was stirred at room temperature for 2h. The mixture was diluted with Et₂O (20 mL) and concentrated under reduced pressure. The crude product was treated with Et₂O (2 x 20 mL) and concentrated under reduced pressure to afford 0.72 g (~100 % yield) of crude product as the HCl salt. This material was used without further purification or characterization.

PREPARATIVE EXAMPLES 126-129

Following the procedure set forth in Preparative Example 100 but using the commercially available N-protected amino acids and amines indicated, the amine hydrochloride products in the Table below were obtained.

Prep Ex.	Amino acid	Amine	Product	Yield (%)
126				68%
127				68%
129				97%

PREPARATIVE EXAMPLE 146

Step A

To a solution of tosylaziridine [*J. Am. Chem. Soc.* 1998, 120, 6844-6845] (0.5 g, 2.1 mmol) and Cu(acac)₂ (55 mg, 0.21 mmol) in THF (5 mL) at 0 °C was added PhMgBr (3.5 ml, 3.0 M in THF) diluted with THF (8 mL) dropwise over 20 min. The resulting solution was allowed to gradually warm to rt and was stirred for 12h. Sat. aq. NH₄Cl (5 mL), was added and the mixture was extracted with Et₂O (3 x 15 mL). The organic layers were combined, washed with brine (1 x 10 mL), dried (MgSO₄) and concentrated under reduced pressure. The crude residue was purified by preparative TLC eluting with hexane/EtOAc (4:1) to afford 0.57 g (86%)

yield) of a white solid. The purified tosylamine was taken on directly to the next step.

Step B


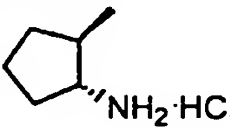

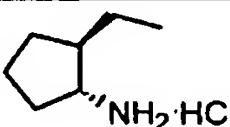

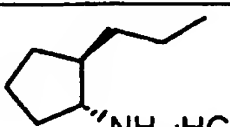
5 To a solution of tosylamine (0.55 g, 1.75 mmol) in NH_3 (20 mL) at -78°C was added sodium (0.40 g, 17.4 mmol). The resulting solution was stirred at -78°C for 2 h whereupon the mixture was treated with solid NH_4Cl and allowed to warm to rt. Once the NH_3 had boiled off, the mixture was partitioned between water (10 mL) and CH_2Cl_2 (10 mL). The layers were separated and the aqueous layer was
10 extracted with CH_2Cl_2 (2 x 10 mL). The organic layers were combined, dried (NaSO_4), and concentrated under reduced pressure to a volume of ~20 mL. 4N HCl in dioxane (5 mL) was added and the mixture was stirred for 5 min. The mixture was concentrated under reduced pressure and the resultant crude residue was recrystallized from EtOH/Et₂O to afford 0.30 g (87% yield) of a white solid.


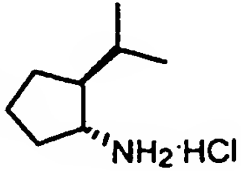
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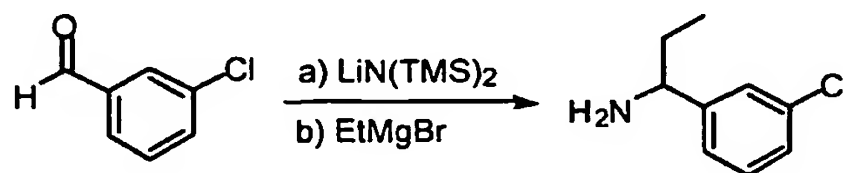
PREPARATIVE EXAMPLES 147-150

Following the procedure set forth in Preparative Example 146 but using the requisite tosylaziridines and Grignard reagents listed in the Table below, the following amine hydrochloride products were obtained.

20

Prep Ex.	Tosyl aziridine	Grignard Reagent	Amine hydrochloride	1.Yield (%)
147		MeMgBr		1. 19%
148		EtMgBr		1. 56%
149		<i>n</i> -PrMgBr		1. 70%

150		<i>i</i> -PrMgCl		1. 41%
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PREPARATIVE EXAMPLE 200

5 To a solution of 3-chlorobenzaldehyde (2.0 g, 14.2 mmol) in THF (5 mL) at 0 °C was added LiN(TMS)₂ (17.0 ml, 1.0 M in THF) dropwise and the resulting solution was stirred for 20 min. EtMgBr (6.0 mL, 3.0 M in Et₂O) was added dropwise and the mixture was refluxed for 24 h. The mixture was cooled to room temperature, poured into sat. aq. NH₄Cl (50 mL), and then extracted with CH₂Cl₂ (3

10 x 50 volumes). The organic layers were combined and concentrated under reduced pressure. The crude residue was stirred with 3 M HCl (25 mL) for 30 min, the aqueous layer was then extracted with CH₂Cl₂ (3 x 15 mL) and the organic layers were discarded. The aqueous layer was cooled to 0 °C and treated with solid NaOH pellets until pH = 10 was obtained. The aqueous layer was extracted with

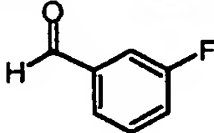
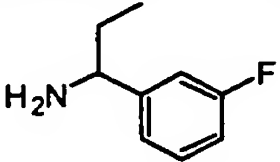
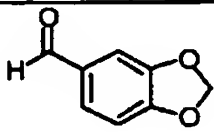
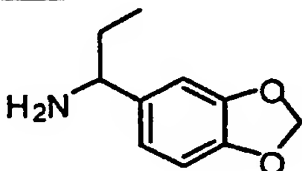
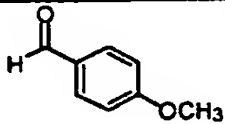
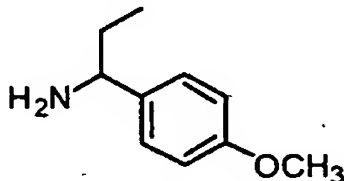
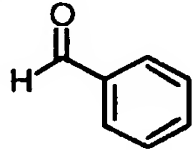
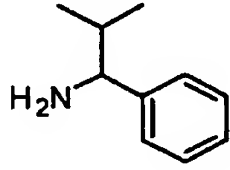
15 CH₂Cl₂ (3 x 15 mL) and the organic layers were combined. The organic layer was washed with brine (1 x 25 mL), dried (Na₂SO₄), and concentrated under reduced pressure to afford 1.6 g (66% yield) of the crude amine as a yellow oil (MH⁺ 170). This material was determined to be >90% pure and was used without further purification.

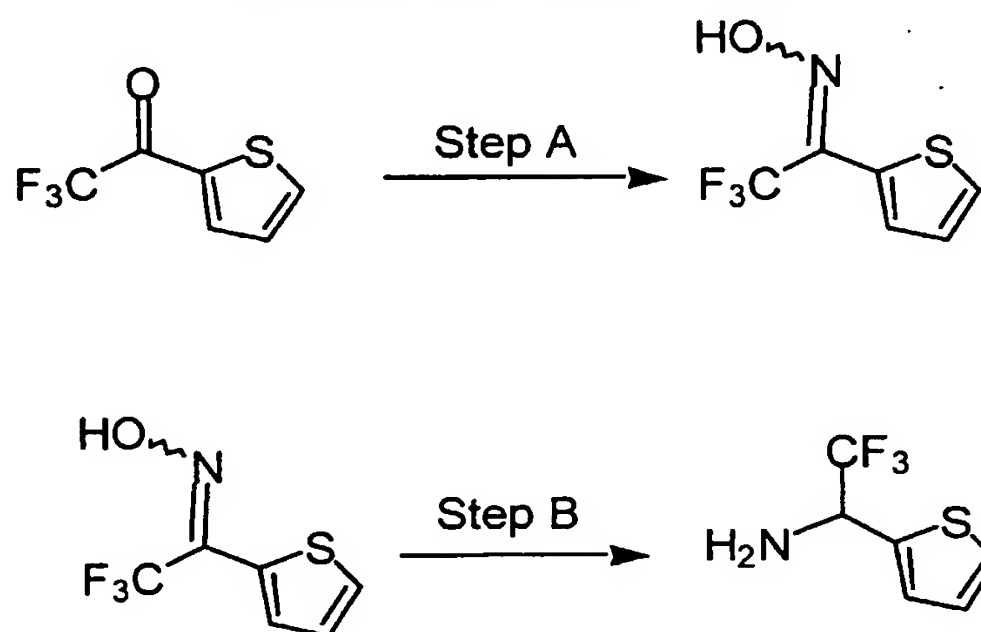
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PREPARATIVE EXAMPLES 207-213

Following the procedure set forth in Preparative Example 200 but using the commercially available aldehydes and Grignard indicated below, the amine products listed in the Table below were obtained.

25

Prep Ex.	Aldehyde	Grignard Reagent	Amine Product	1. Yield (%) 2. MH ⁺
207		EtMgBr		1. 73% 2. 154
209		EtMgBr		1. 55% 2. 180
211		EtMgBr		1. 80% 2. 166
213		i-PrMgBr		1. 20% 2. 150

PREPARATIVE EXAMPLE 250

Step A

A mixture of 2-(trifluoroacetyl)thiophene (2 mL, 15.6 mmol), hydroxylamine hydrochloride (2.2 g, 2 eq), Diisopropylethylamine (5.5 mL, 2 eq) and MeOH (50 mL) was stirred at reflux for 48-72 hrs, then concentrated in vacuo. The residue was diluted with EtOAc, washed with 10% KH_2PO_4 and dried over Na_2SO_4 (anhydrous). Filtration and concentration afforded the desired oxime (2.9 g, 96%) which was used directly in Step B without further purification.

Step B

10

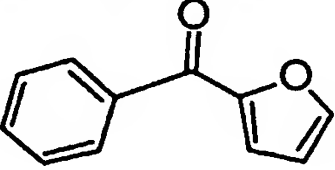
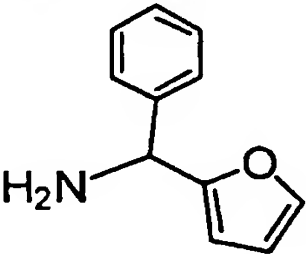
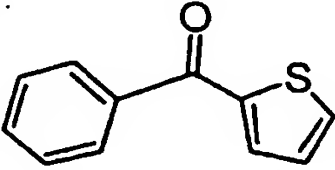
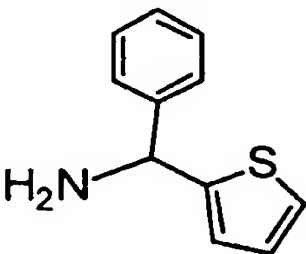
To a mixture of the product from Step A above in TFA (20 mL) was added Zn powder (3 g, 3 eq) portionwise over 30 min. The mixture was stirred at room temperature overnight. The solid was filtered and the mixture reduced under vacuo. Aqueous NaOH (2 M) was added and the mixture was extracted several times with CH_2Cl_2 . The organic phase was dried over anhydrous Na_2SO_4 , filtered and concentrated to afford the title compound (1.4 g, 50%).

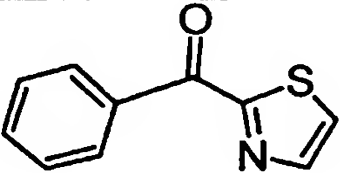
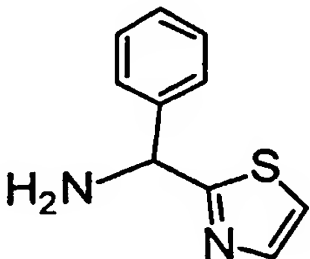
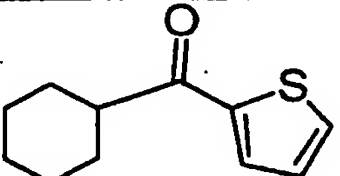
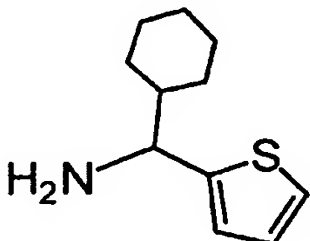
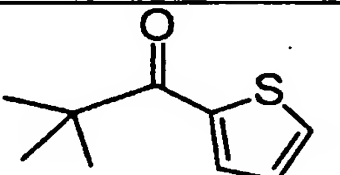
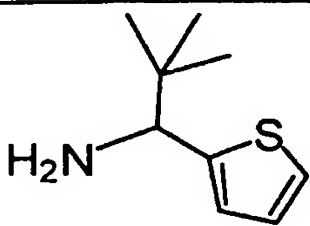
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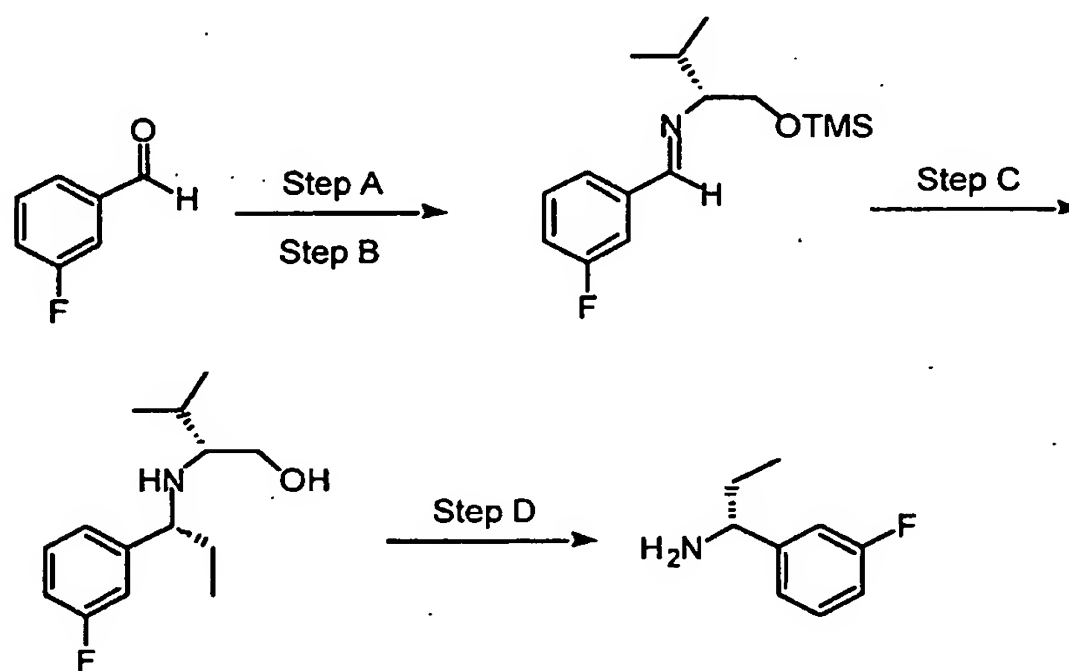
PREPARATIVE EXAMPLES 255-259

20

Following the procedure set forth in Preparative Example 250 but using the commercially available ketones indicated below, the amine products listed in the table below were obtained.

Prep Example	Ketone	Amine Product	1. Yield (%) 2. MH^+
255			1. 47% 2. 174
256			1. 71% 2. 190

257			1. 78% 2. 191
258			1. 80% 2. 190
259			1. 9% 2. 156

PREPARATIVE EXAMPLE 2705 Step A

To a solution of (D)-valinol (4.16 g, 40.3 mmol) in CH₂Cl₂ (60 mL) at 0 °C was added MgSO₄ (20 g) followed by dropwise addition of 3-fluorobenzaldehyde (5.0 g, 40.3 mmol). The heterogenous solution was stirred at 0°C for 2h, was allowed to warm to room temperature and was stirred overnight (14h). The mixture was filtered and the drying agent was washed with CH₂Cl₂ (2 x 10 mL). The filtrate

was concentrated under reduced pressure to afford 8.4 g (100%) of a colorless oil which was taken onto the next step without further purification.

Step B

5 To a solution of the imine (8.4 g, 40.2 mmol) from Step A in CH_2Cl_2 (60 mL) at room temperature was added Et_3N (6.2 mL, 44.5 mmol) followed by dropwise addition of TMSCl (5.7 mL, 44.5 mmol). The mixture was stirred for 6h at room temperature whereupon the precipitate that had formed was filtered off and washed with CH_2Cl_2 (2 x 10 mL). The combined filtrate was concentrated under reduced
10 pressure and was taken up in Et_2O /hexane (1:1/150 mL). The precipitate was filtered off and the filtrate was concentrated under reduced pressure to afford 10.1 g (89%) of the protected imine as a red oil. This material was taken onto the next step without further purification.

Step C

15 To a solution of EtI (4.0 g, 25.6 mmol) in Et_2O (40 mL) at -78°C was added $t\text{-BuLi}$ (30.1 mL, 51.2 mmol, 1.7 M in pentane) and the mixture was stirred for 10 min. The mixture was warmed to room temperature, stirred for 1 h, and was recooled to -40°C . A solution of the imine (6.0 g, 21.4 mmol) from Step B in Et_2O
20 (30 mL) was added dropwise via addition funnel to afford a bright orange mixture. The reaction mixture was stirred for 1.5 h at -40°C whereupon 3M HCl (50 mL) was added and the mixture was allowed to warm to room temperature. Water (50 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 30 mL) and the organic layers were combined and discarded. The
25 aqueous layer was cooled to 0°C and carefully treated with solid NaOH pellets until $\text{pH} = 12$ was obtained. The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined layers were washed with brine (1 x 30 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford 4.8 g (94% yield) of the amine as a red oil. This material was taken on crude to the next
30 step without further purification.

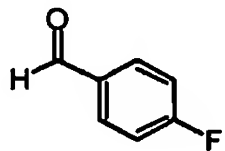
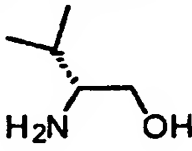
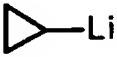
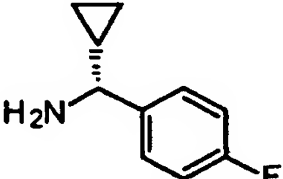
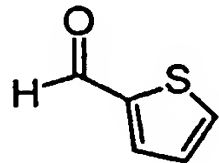
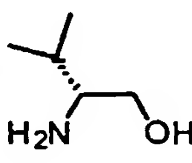
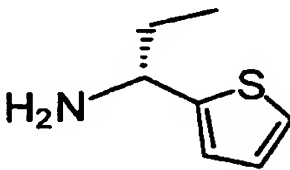
Step D

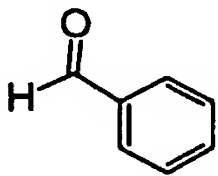
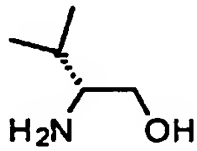
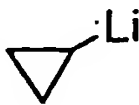
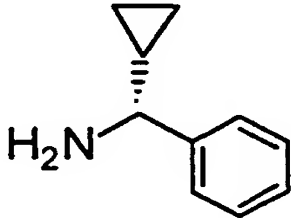
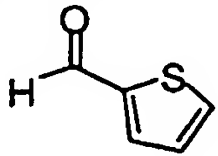
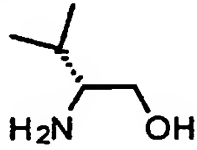
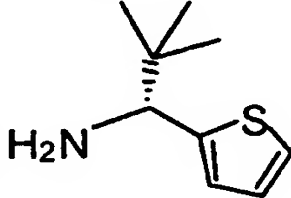
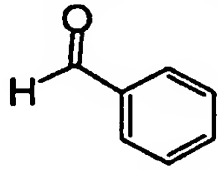
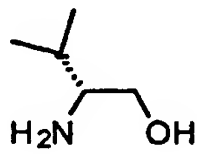
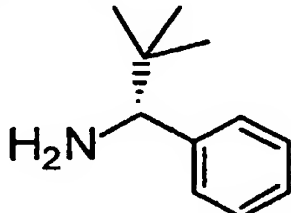
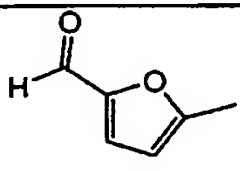
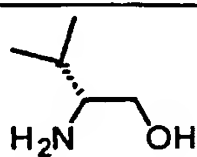
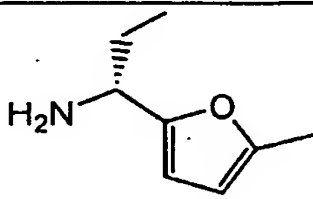
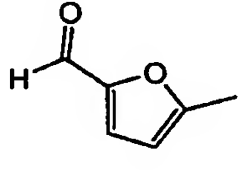
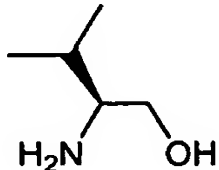
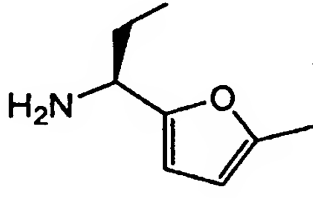
 To a solution of amine (4.5 g, 18.8 mmol) from Step C in MeOH (80 mL) at room temperature was added MeNH_2 (25 mL, 40% in water) followed by the

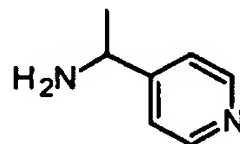
addition of a solution of H_5IO_6 (14.0 g, 61.4 mmol) in H_2O (25 mL). The heterogenous mixture was stirred for 1.5 h (until the reaction was complete by TLC) and the precipitate was filtered off. The resulting filtrate was diluted with water (50 mL) and the mixture was extracted with Et_2O (4 x 60 mL). The combined organic layers were concentrated to a volume of ~30 mL whereupon 3M HCl (75 mL) was added. The mixture was stirred overnight (12h at room temperature) whereupon the mixture was concentrated to remove the volatiles. The aqueous layer was extracted with Et_2O (3 x 40 mL) and the organic layers were discarded. The aqueous layer was cooled to 0°C and was carefully treated with solid NaOH pellets until pH ~12 was reached. The aqueous layer was extracted with Et_2O (3 x 60 mL) and the combined organic layers were dried (MgSO_4). The organic layer was concentrated under reduced pressure to afford 2.8 g (97% yield) of the desired amine as a yellow oil [MH^+ 154]. This compound was proven to be >85% pure by ^1H NMR and was used without further purification.

PREPARATIVE EXAMPLES 273-280

Following the procedure set forth in Preparative Example 270 but using the commercially available aldehydes, amino alcohols, and organolithium reagents indicated below, the optically pure amine products in the Table below were obtained.

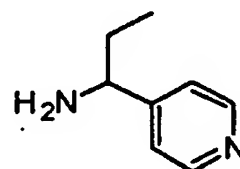
Prep Ex.	Aldehyde	Amino Alcohol	Organo lithium	Product	1. Yield (%) 2. MH^+
273					1. 54% 2. 166
276			EtLi		1. 42% 2. 142

278					1. 62% 2. 148
279			t-BuLi		1. 27% 2. 256
280			t-BuLi		1. 15% 2. 164
280.1			EtLi		1. 29% 2. 126
280.2			EtLi		1. 35% 2. 126

PREPARATIVE EXAMPLE 282

5

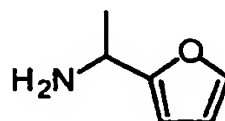
The title compound was prepared according to methods previously described: J. Med. Chem. 1996, 39, 3319-3323.

PREPARATIVE EXAMPLE 284

119

The title compound was prepared according to methods previously described: J. Med. Chem. 1996, 39, 3319-3323.

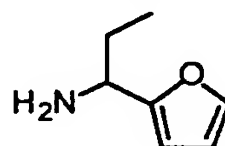
PREPARATIVE EXAMPLE 286



5

The title compound was prepared according to methods previously described: Chem. Pharm. Bull. 1991, 39, 181-183.

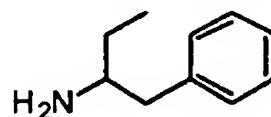
PREPARATIVE EXAMPLE 288



10

The title compound was prepared according to methods previously described: Chem. Pharm. Bull. 1991, 39, 181-183.

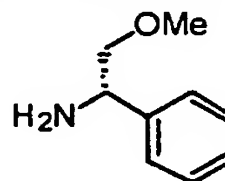
PREPARATIVE EXAMPLE 290



15

The title compound was prepared according to methods previously described: J. Med. Chem. 1988, 31, 2176-2186.

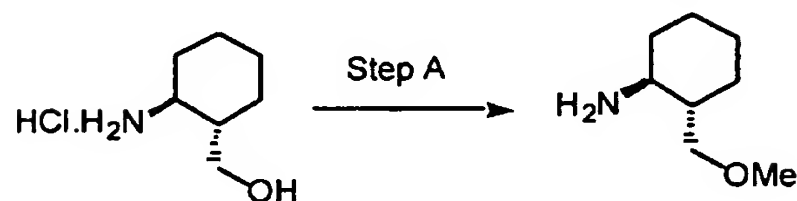
PREPARATIVE EXAMPLE 292



20

The title compound was prepared according to methods previously described: J. Org. Chem. 1978, 43, 892-898.

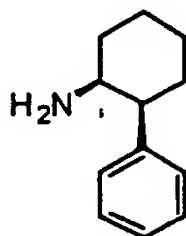
120
PREPARATIVE EXAMPLE 300



Step A

To a solution of KH (0.45 g, 11.3 mmol) in THF (15 mL) at room temperature
5 was added amine hydrochloride (0.85 g, 5.1 mmol) portionwise to afford a
heterogenous reaction mixture. The mixture was allowed to stand overnight (12h)
and then a solution of MeI (0.32 mL, 5.1 mmol) was added dropwise. The mixture
was stirred for 6h whereupon the mixture was carefully poured into cold brine (125
mL). The mixture was extracted with Et₂O (3 x 25 mL) and the organic layers were
10 combined. The organic layer was dried over Na₂SO₄, filtered, and concentrated
under reduced pressure to afford the crude product as a yellow oil. This material
was used without further purification or characterization.

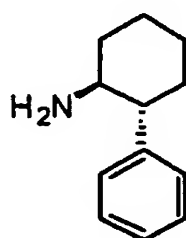
PREPARATIVE EXAMPLE 320



15

The title compound was prepared according to methods previously
described: J. Org. Chem. 1987, 52, 4437-4444.

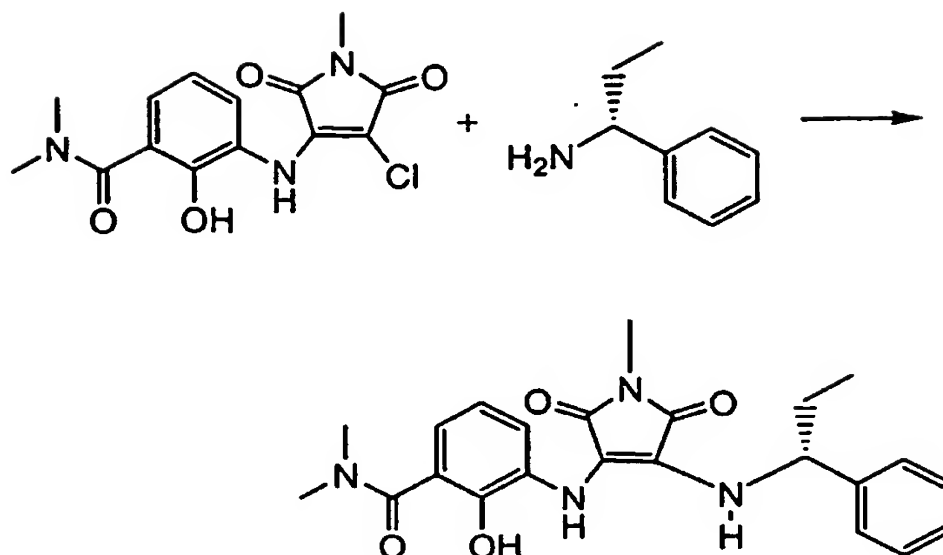
PREPARATIVE EXAMPLE 325



20

The title compound was prepared according to methods previously
described: Bull. Chem. Soc. Jpn. 1962, 35, 11-16.

121
EXAMPLE 500

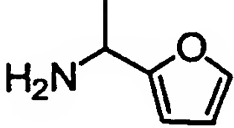
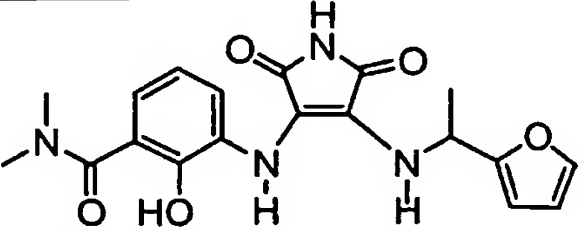
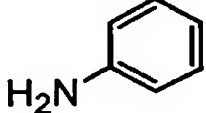
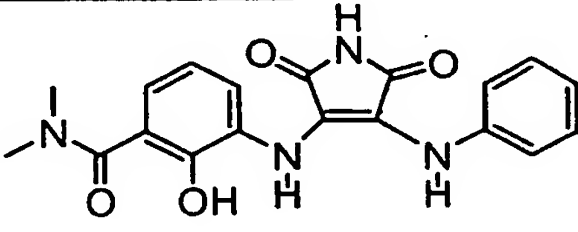
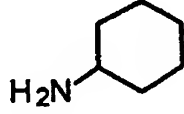
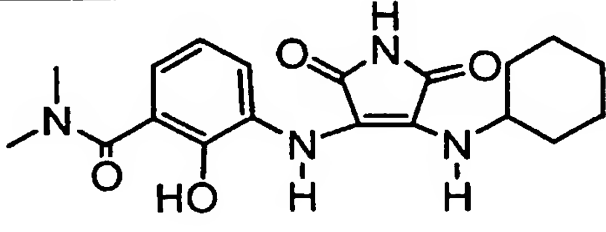
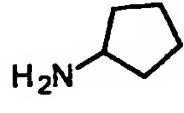
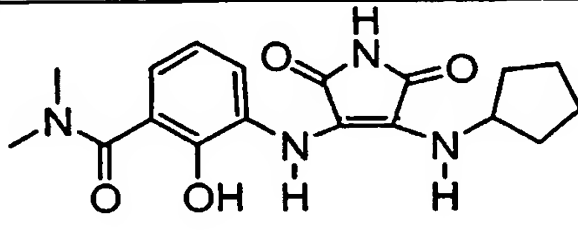
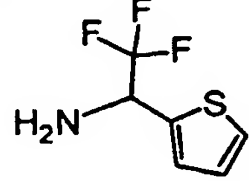
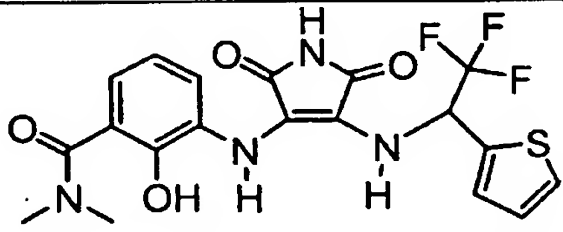
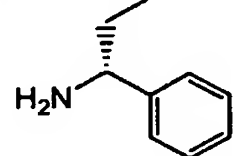
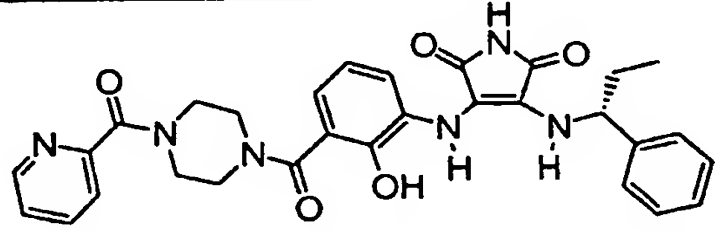
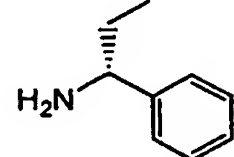
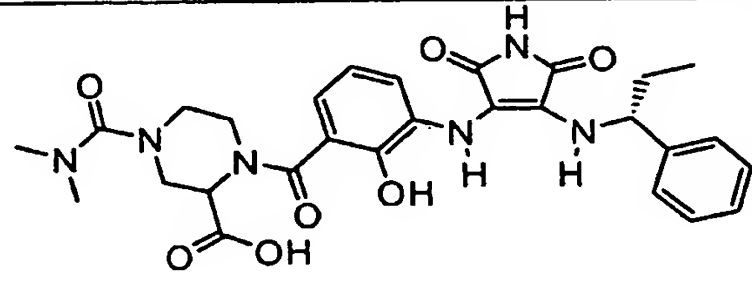
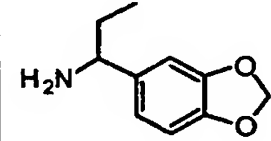
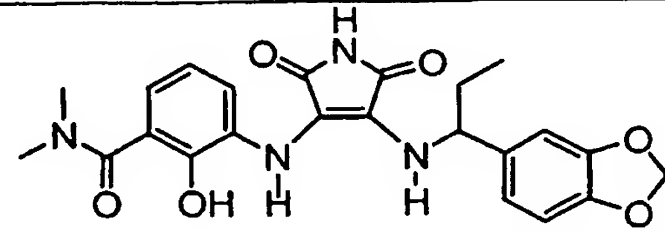


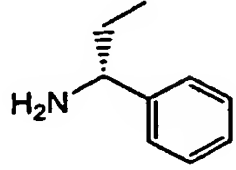
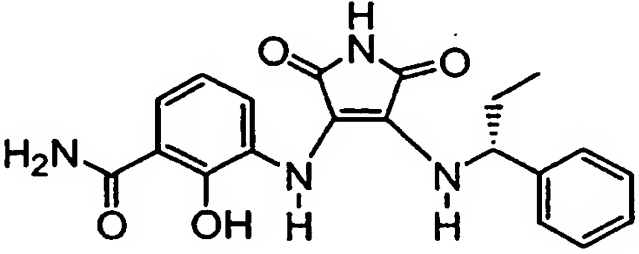
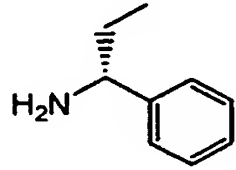
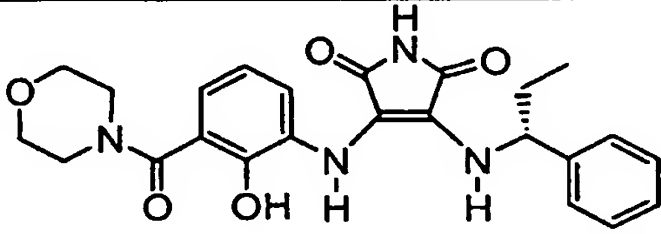
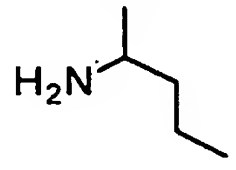
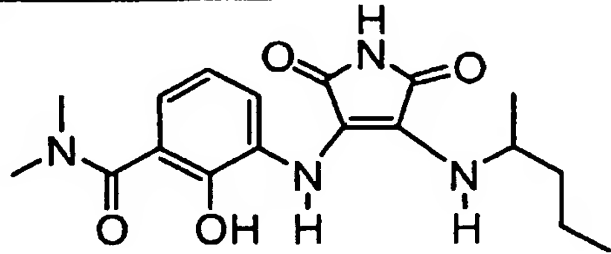
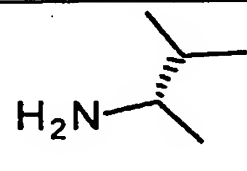
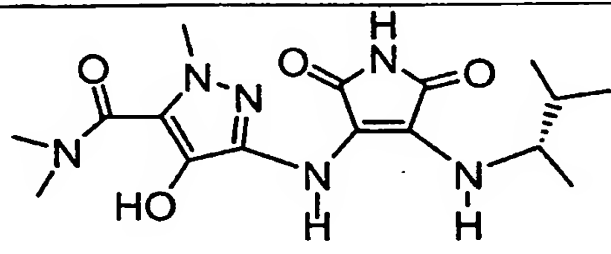
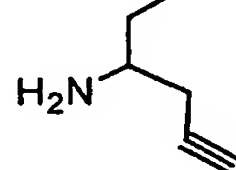
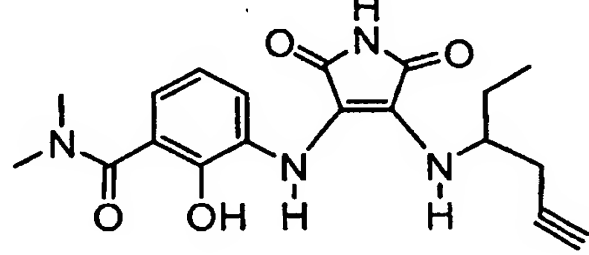
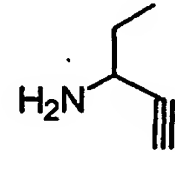
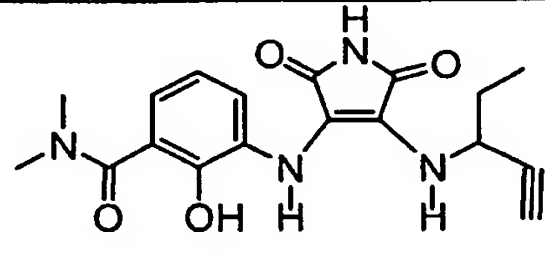
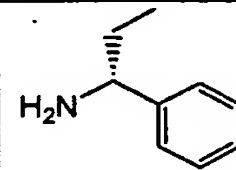
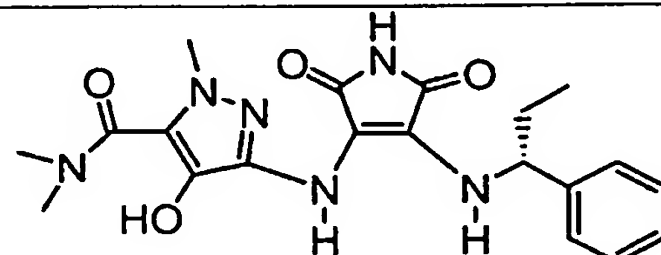
5 If one were to follow the procedure set forth in Pol. J. Chem.1991, 65, 889-897 or the procedure set forth in J. Organomet. Chem. 1994, 482, 85-92 using the chloro intermediate from PREPARATIVE EXAMPLE 67 and the benzyl amine shown, then one would obtain the title compound.

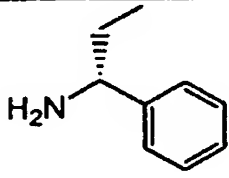
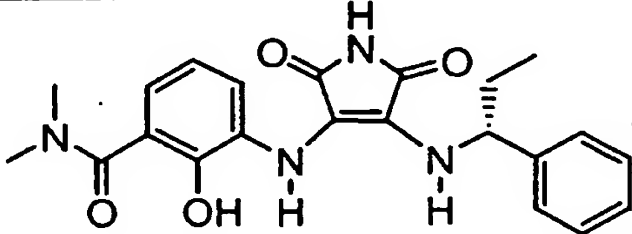
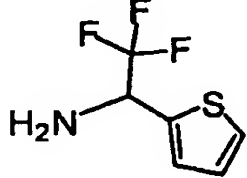
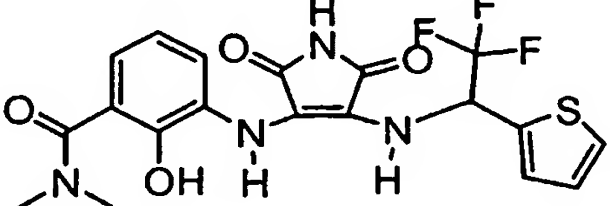
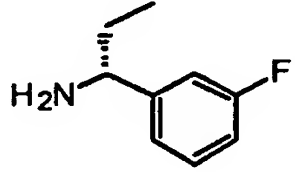
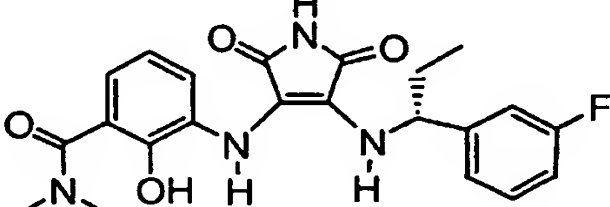
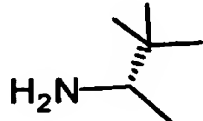
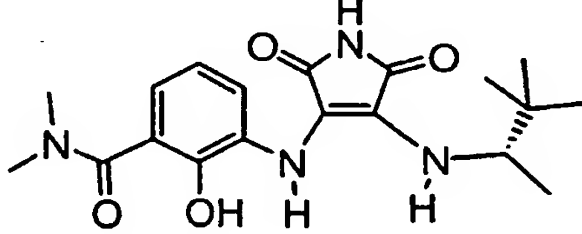
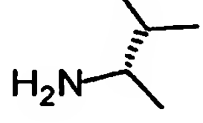
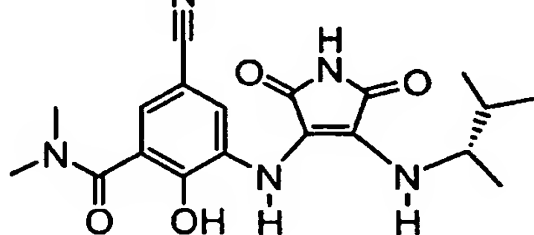
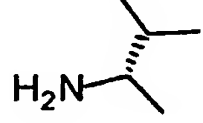
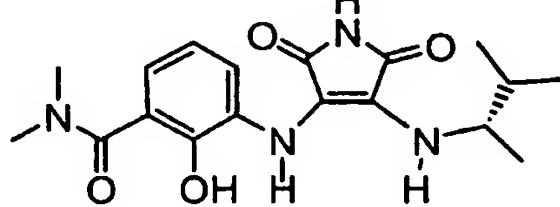
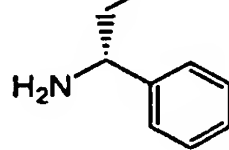
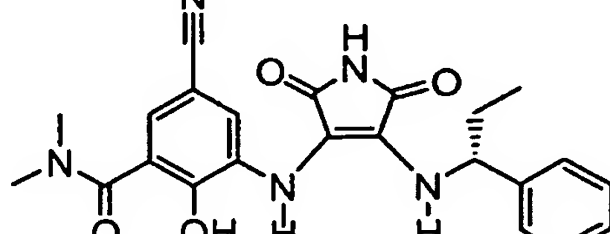
EXAMPLES 501-697

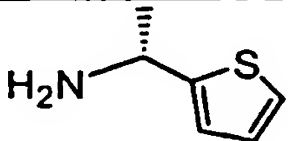
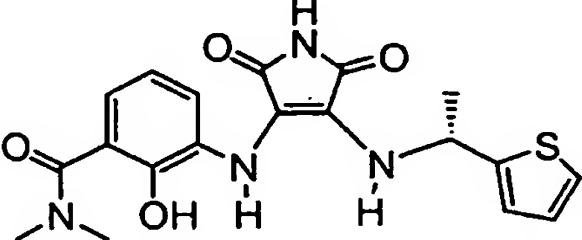
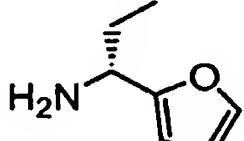
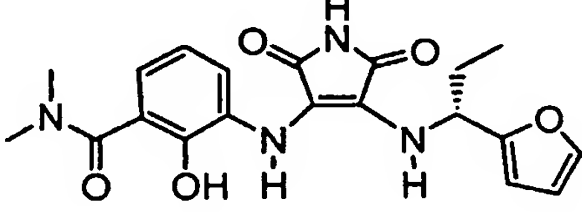
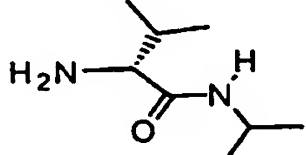
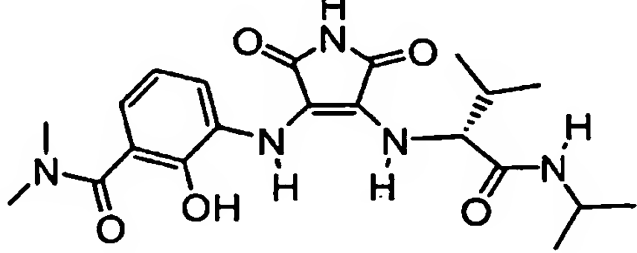
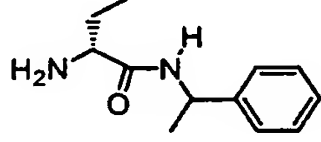
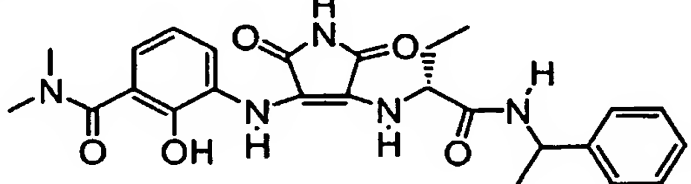
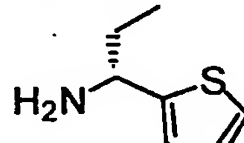
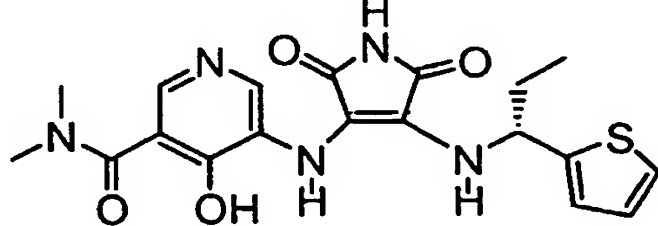
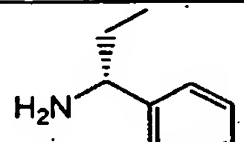
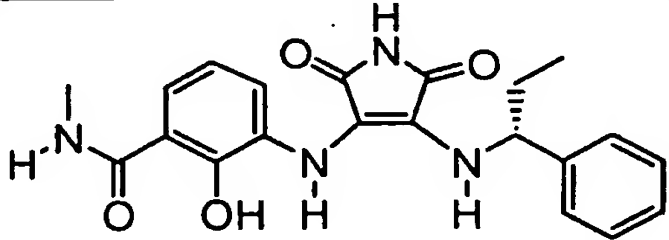
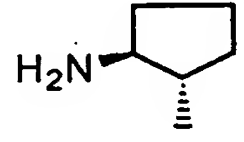
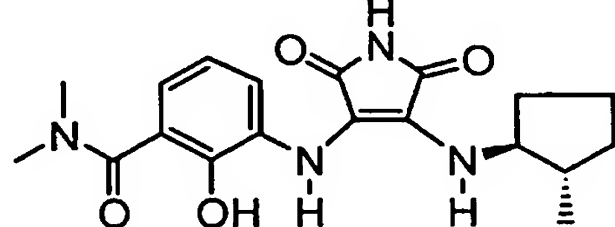
10 If one were to follow the procedure set forth in Example 500 using the prepared (as indicated) or commercially available amines below and the chloro intermediates from the Preparative Examples indicated, the Product listed in the table below would be obtained.

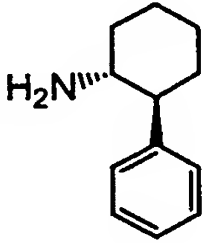
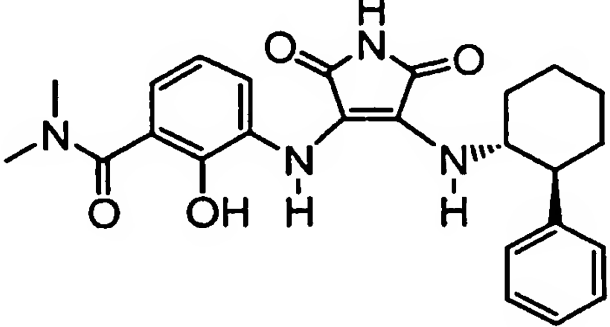
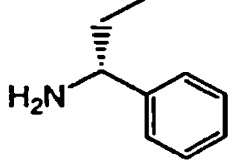
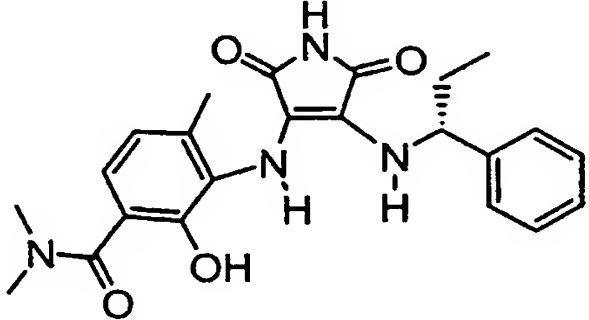
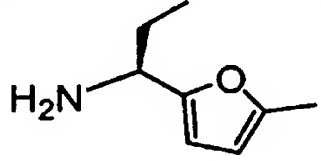
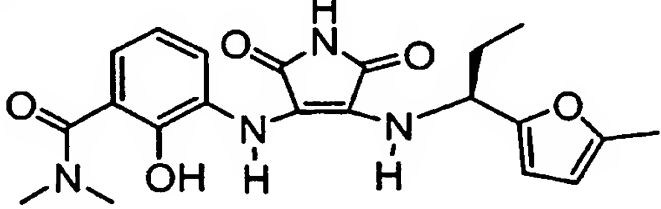
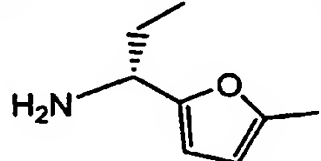
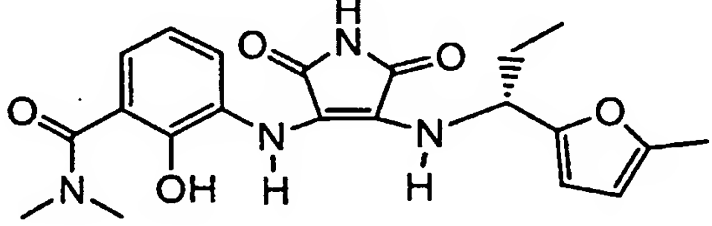
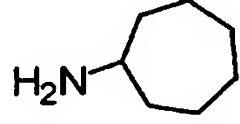
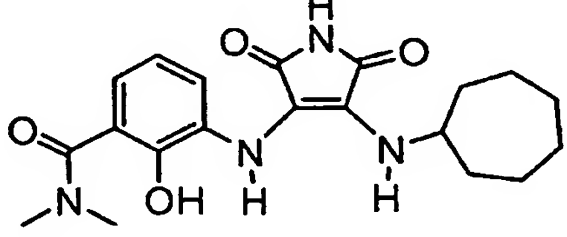
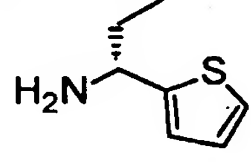
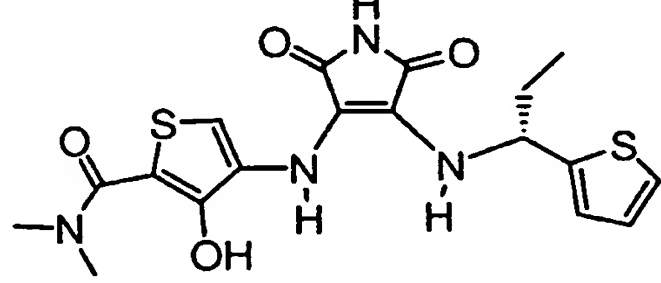
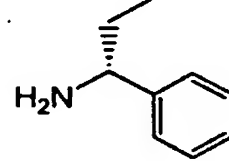
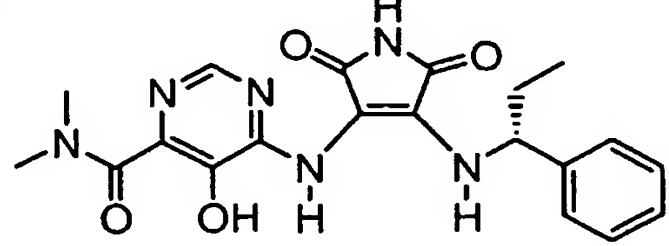
Ex. #	Amine (Prep Ex. #)	Cl Inter. (Prep Ex. #)	Product
501		51	
502		51	

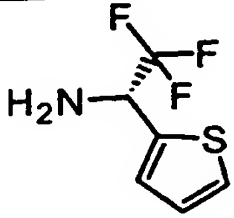
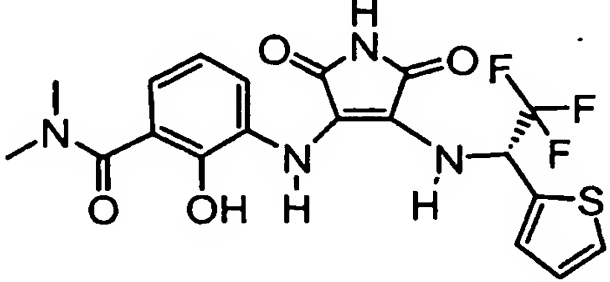
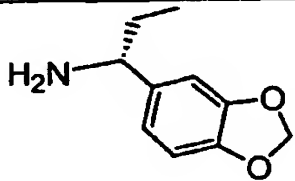
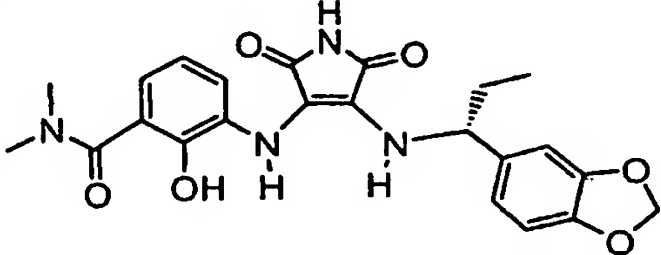
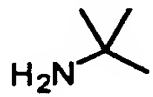
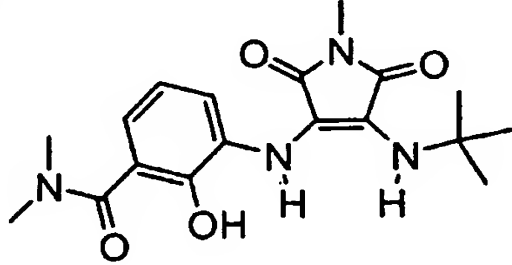
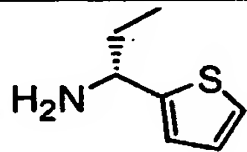
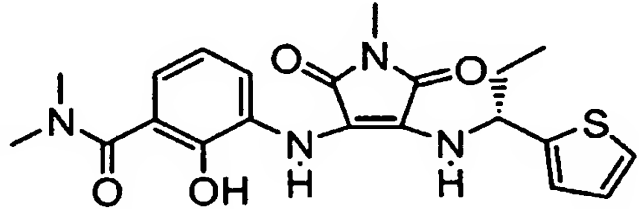
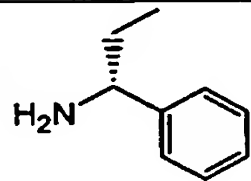
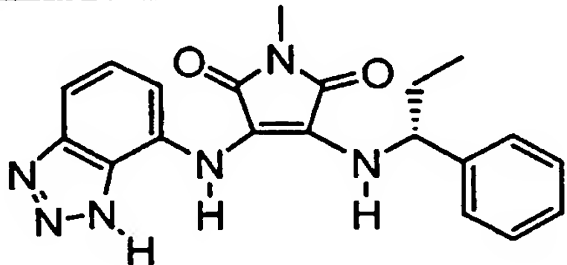
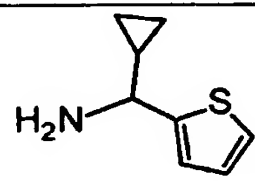
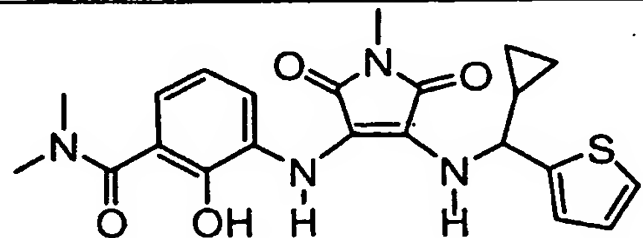
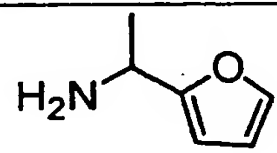
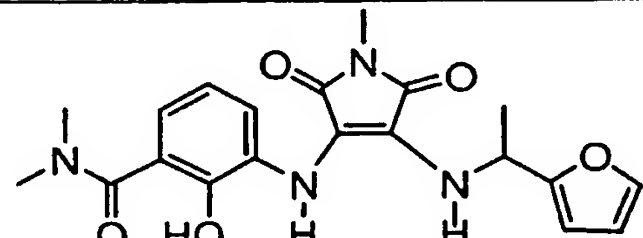
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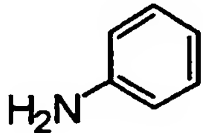
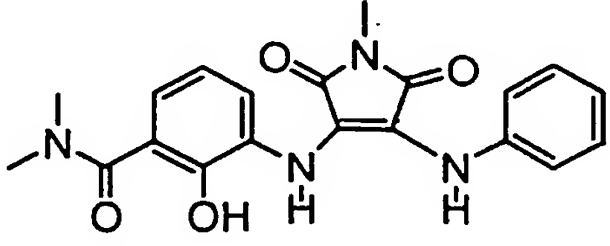
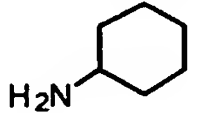
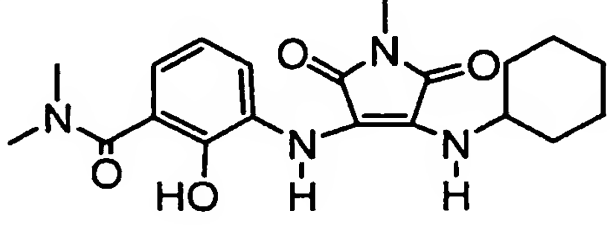
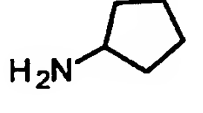
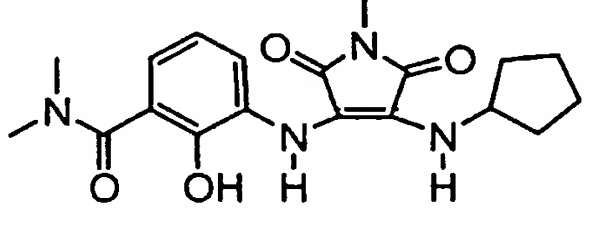
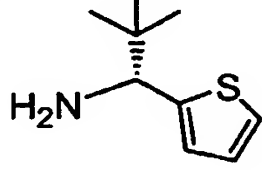
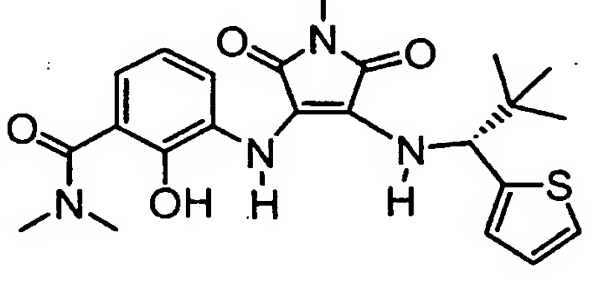
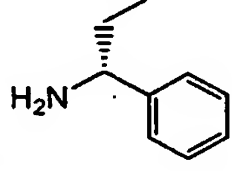
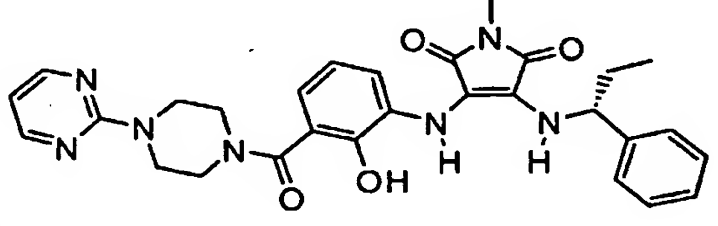
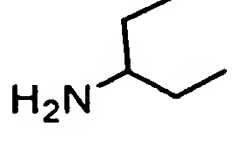
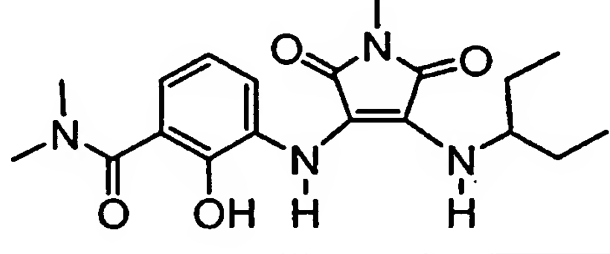
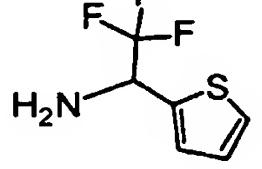
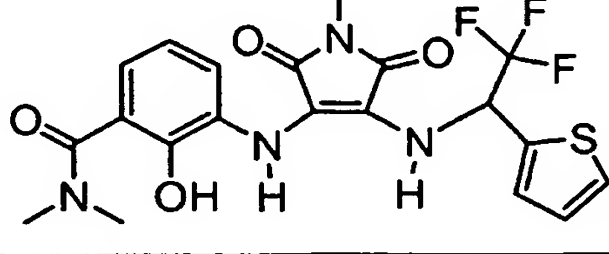
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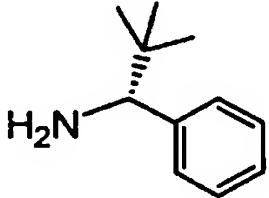
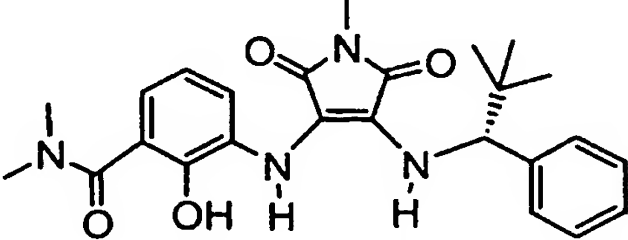
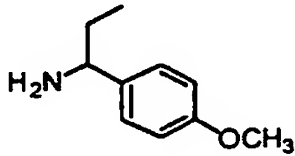
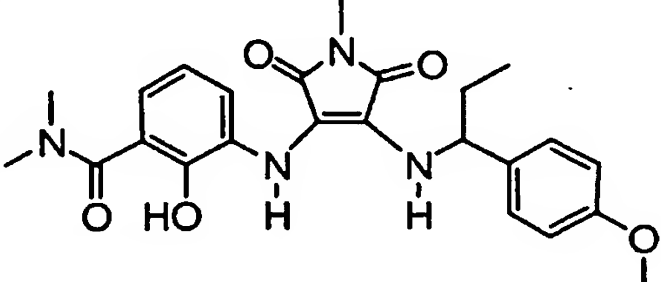
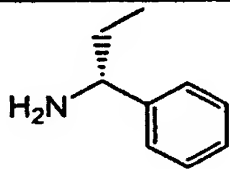
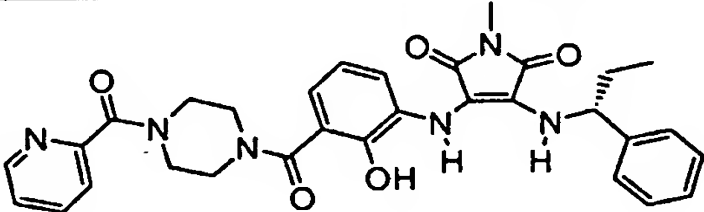
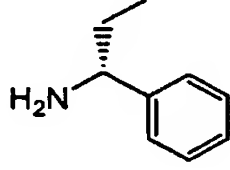
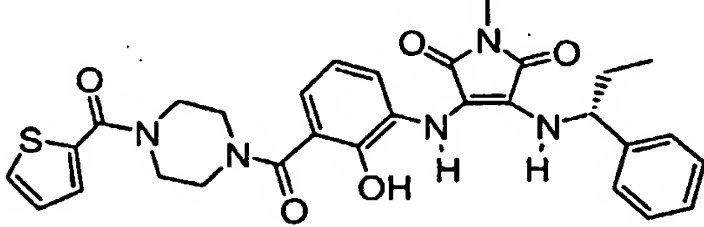
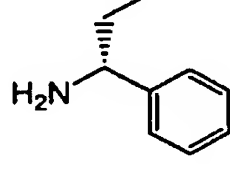
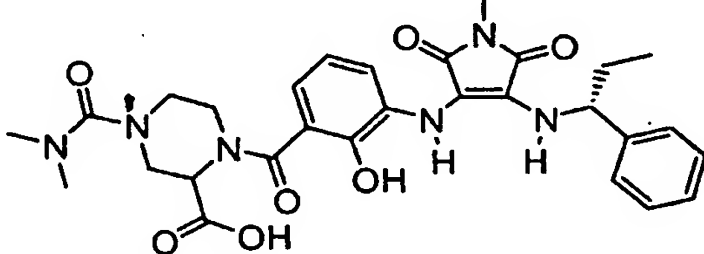
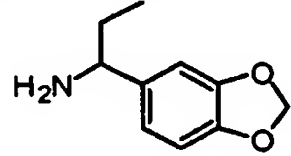
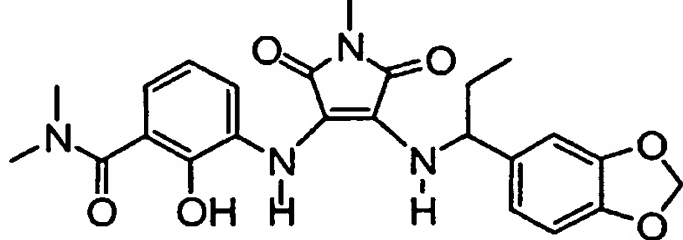
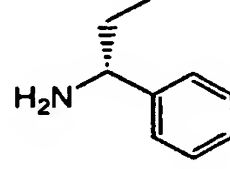
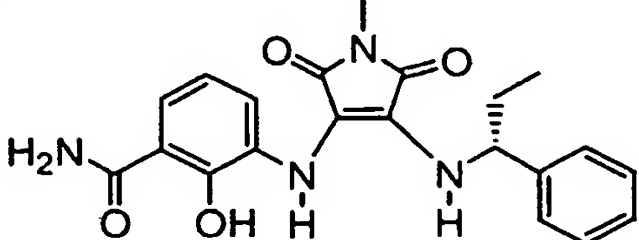
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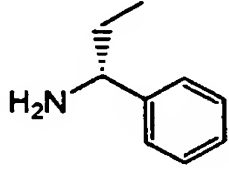
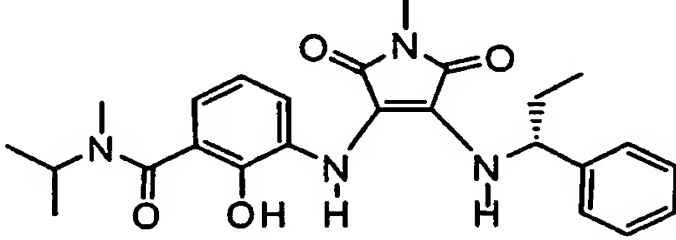
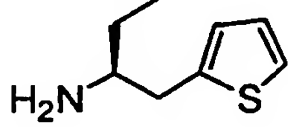
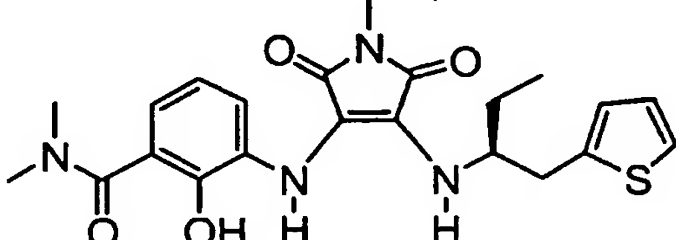
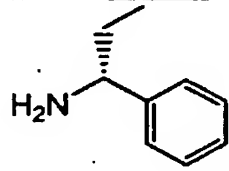
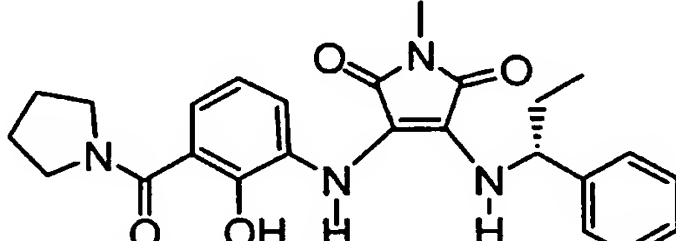
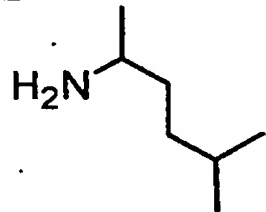
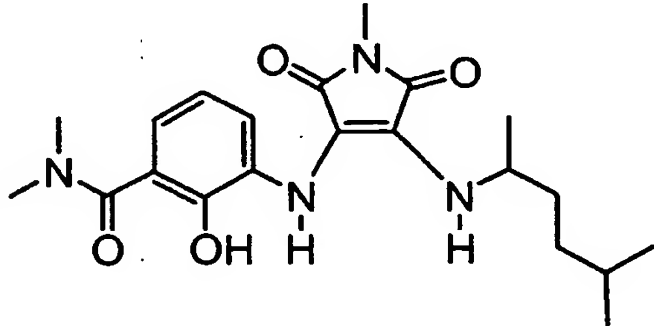
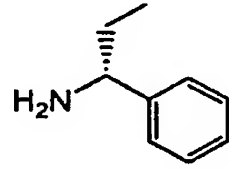
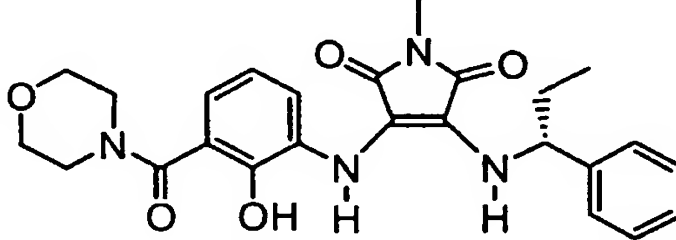
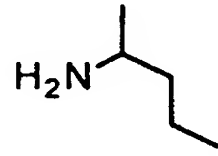
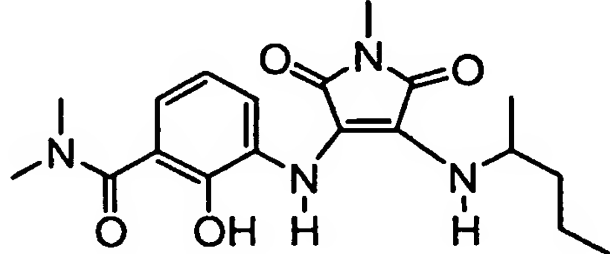
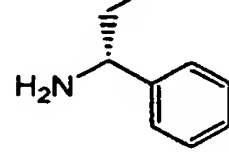
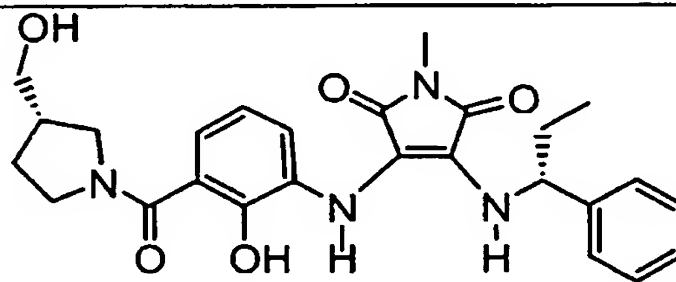
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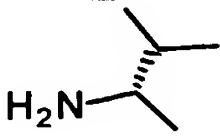
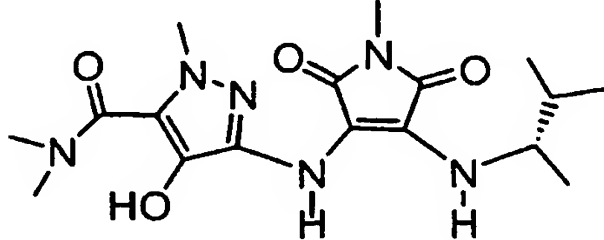
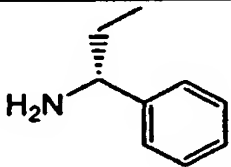
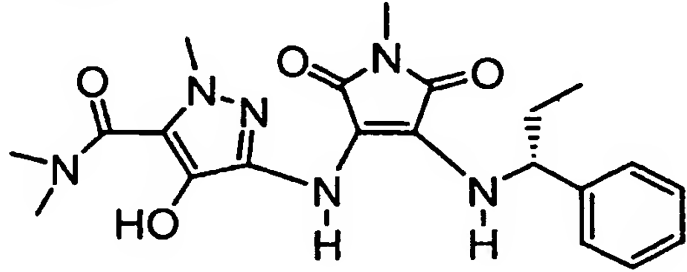
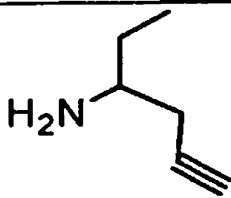
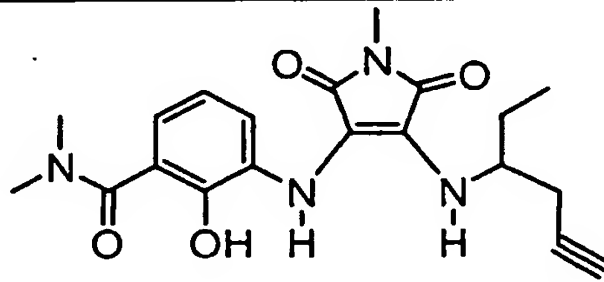
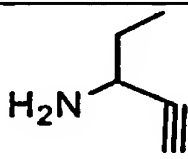
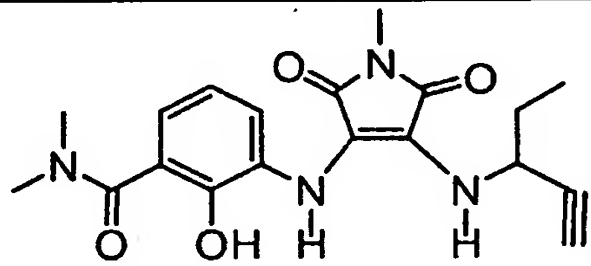
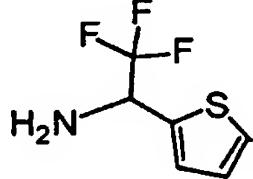
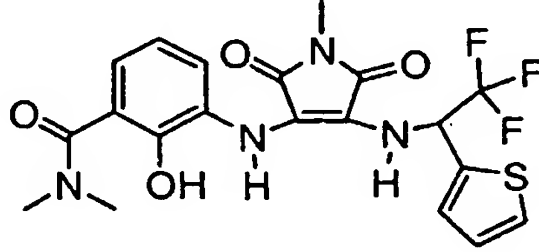
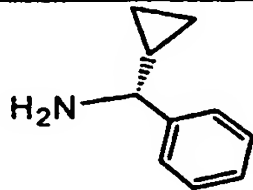
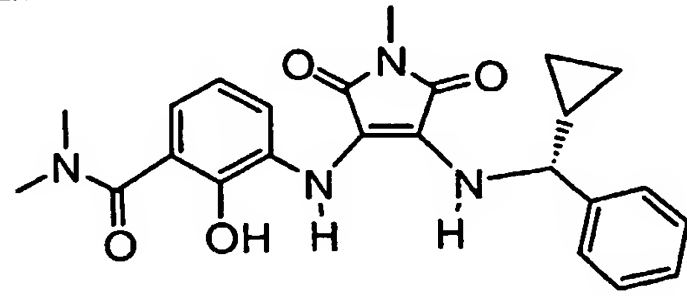
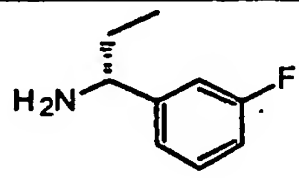
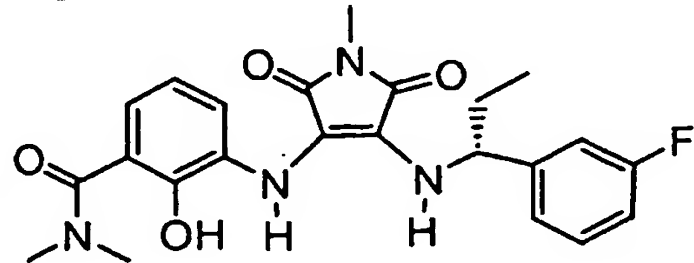
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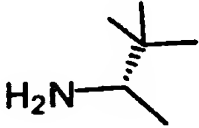
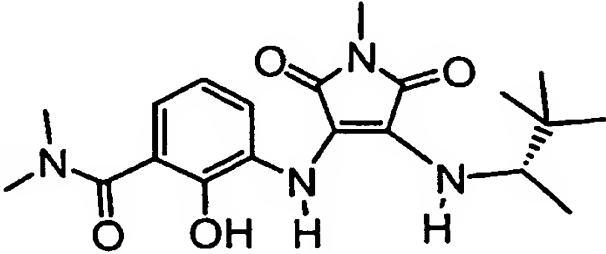
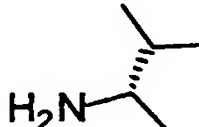
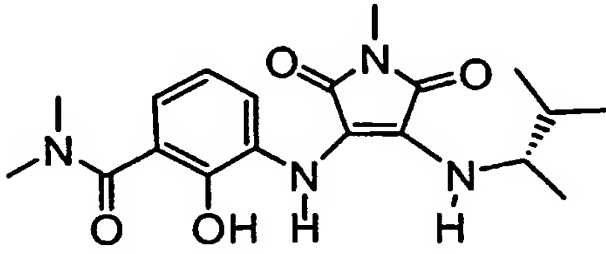
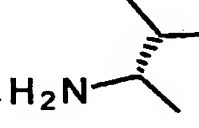
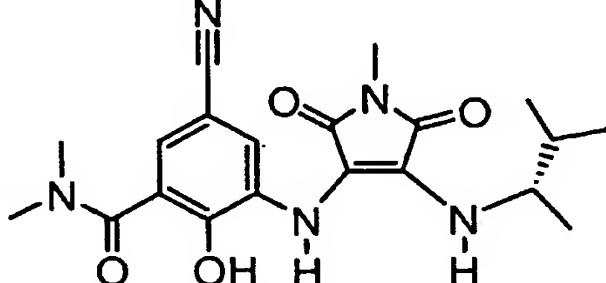
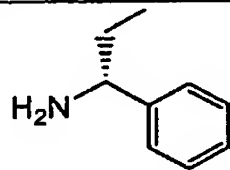
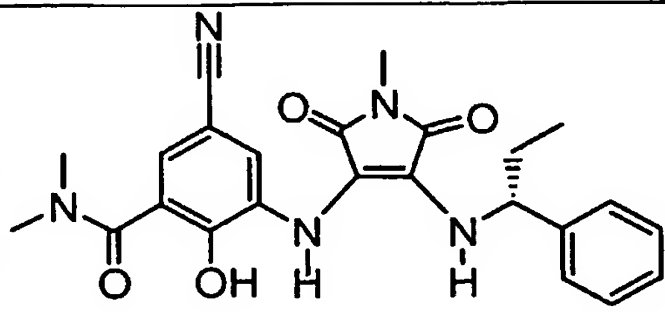
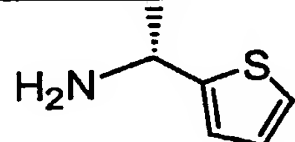
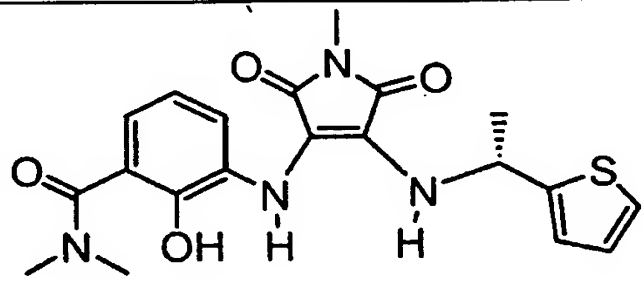
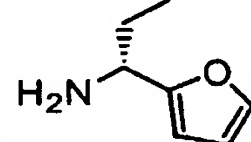
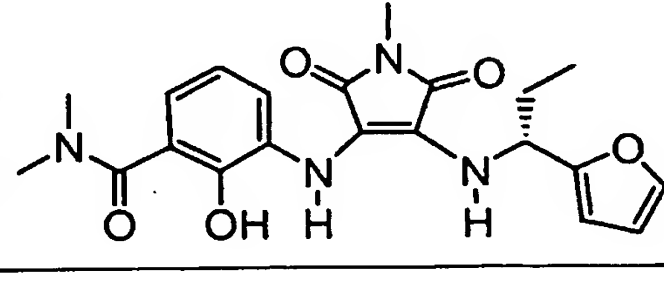
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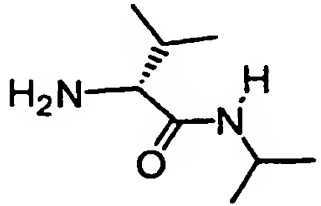
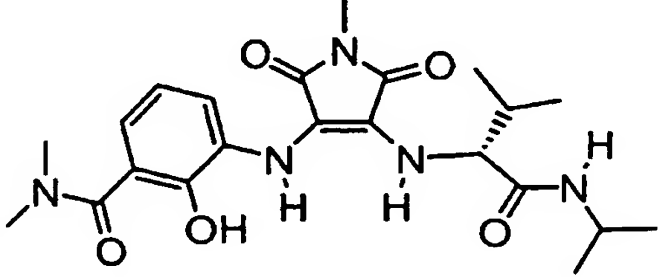
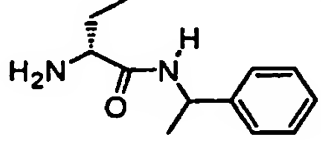
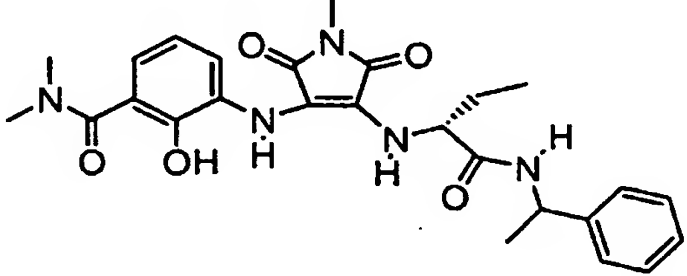
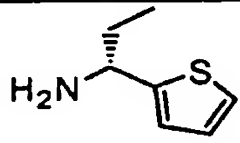
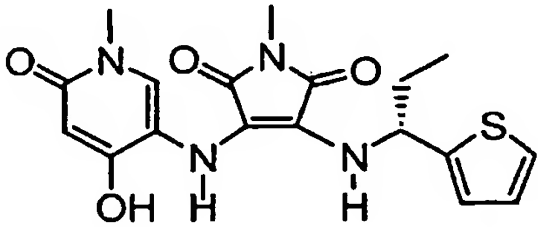
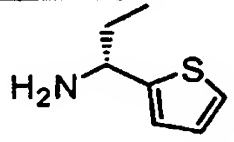
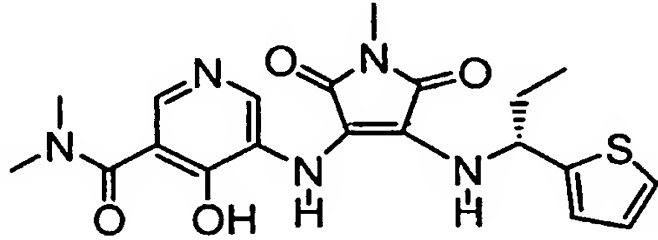
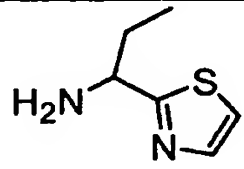
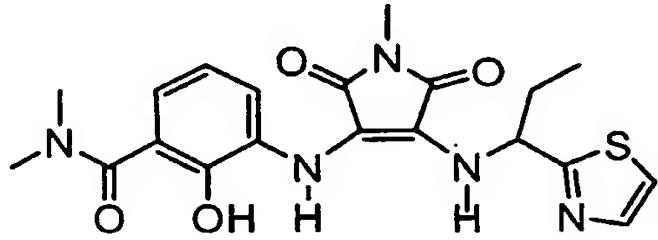
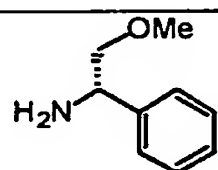
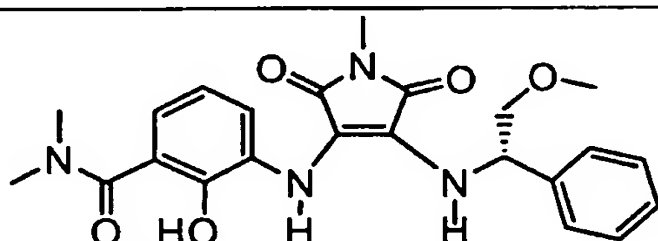
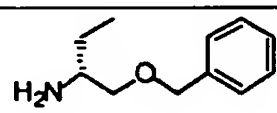
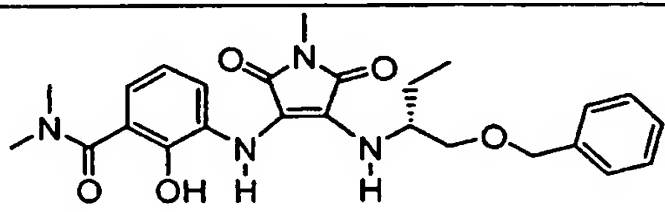
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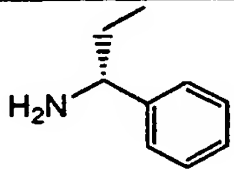
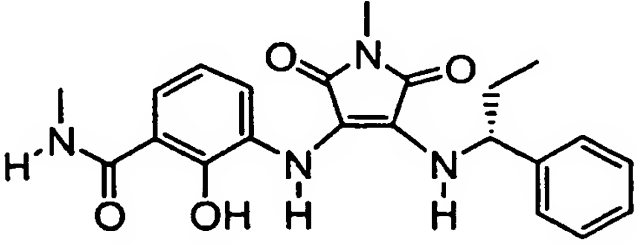
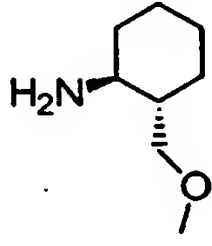
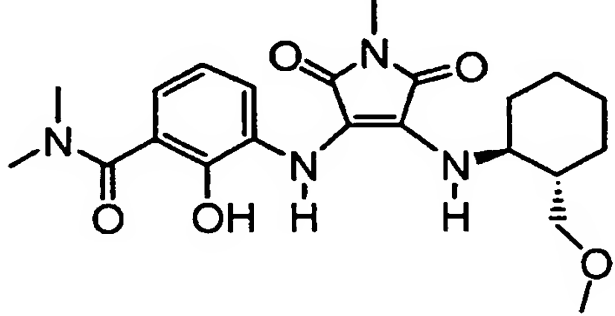
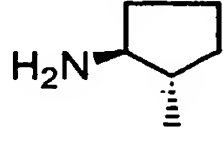
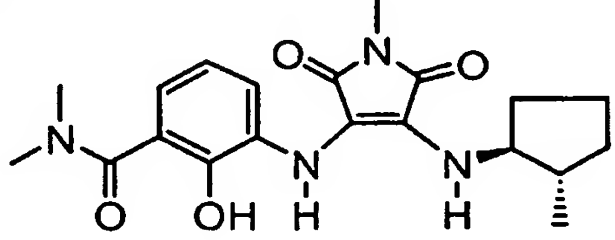
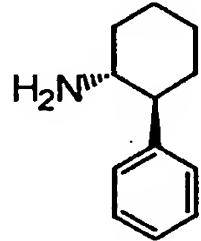
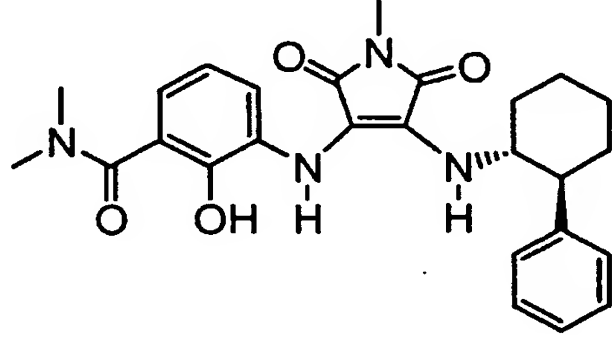
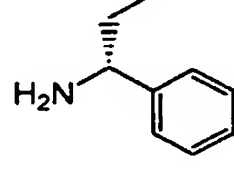
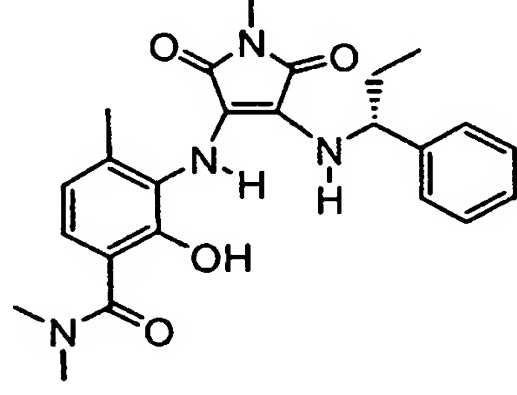
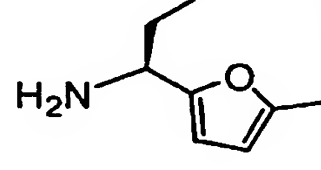
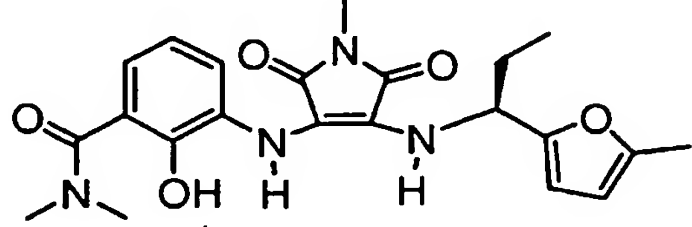
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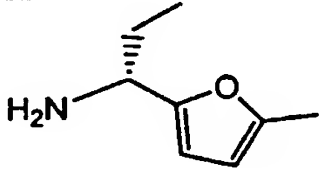
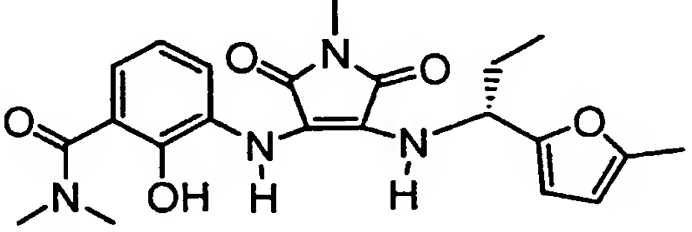
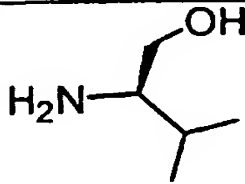
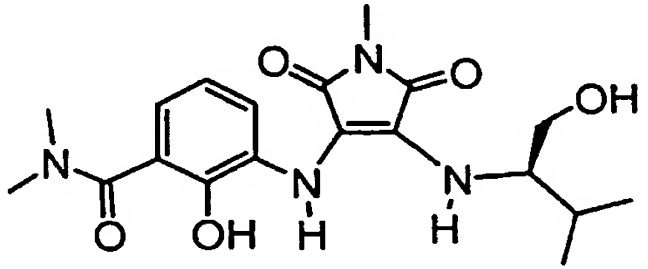

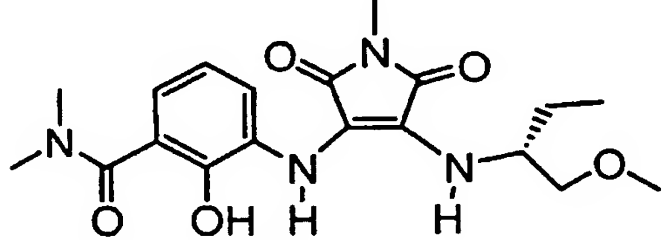
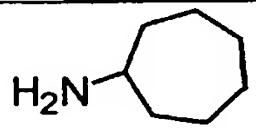
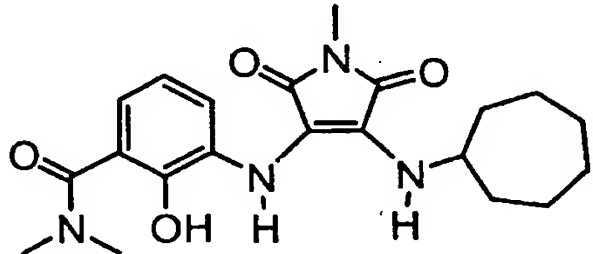
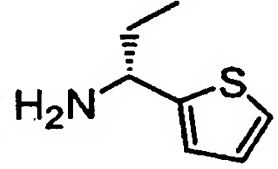
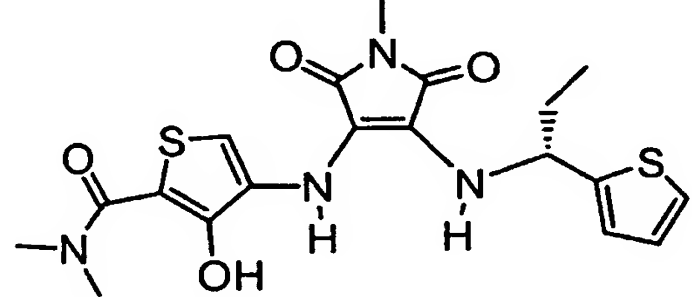
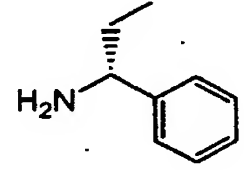
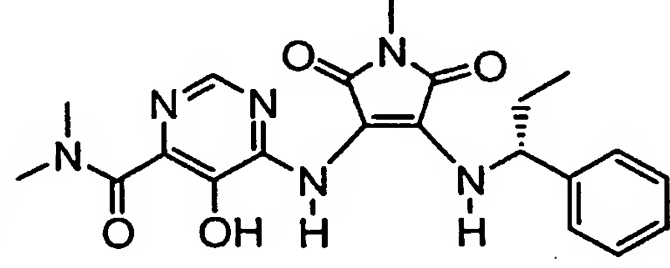
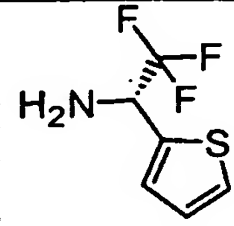
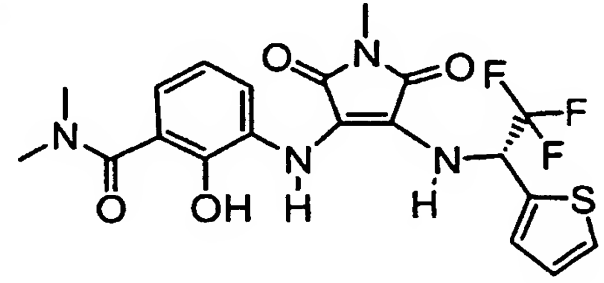
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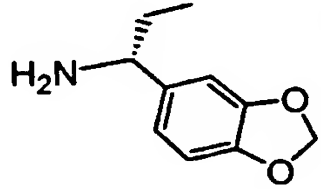
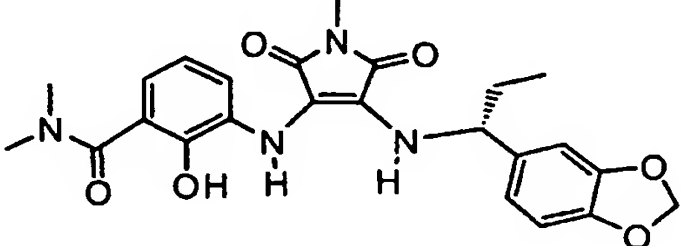
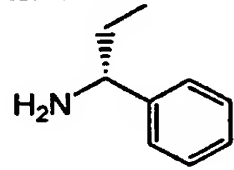
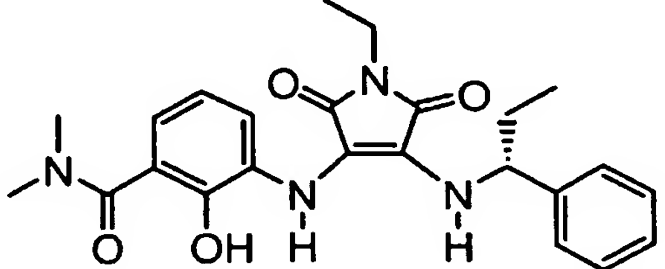
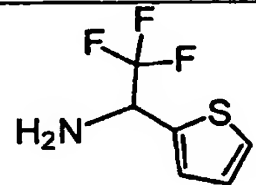
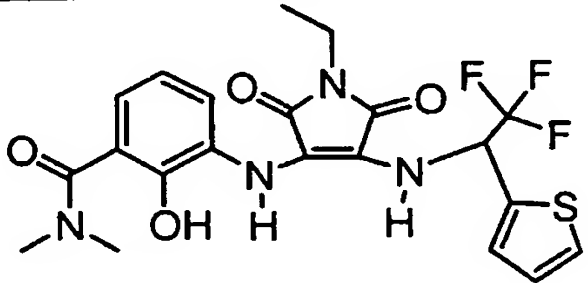
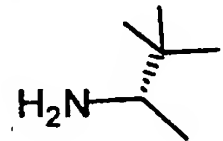
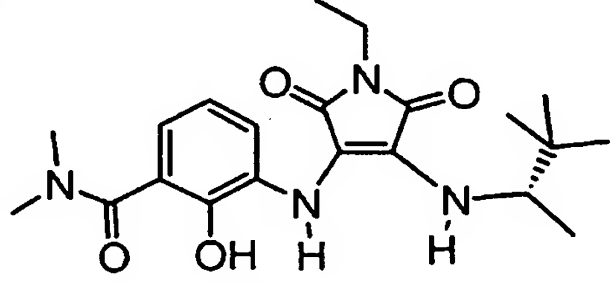
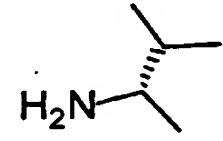
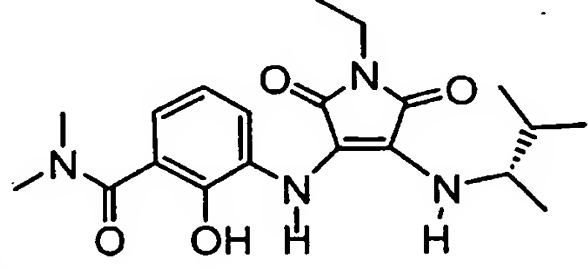
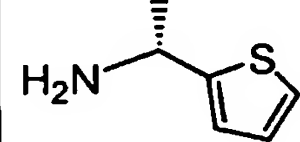
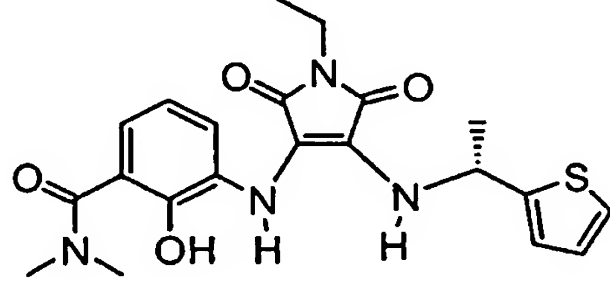
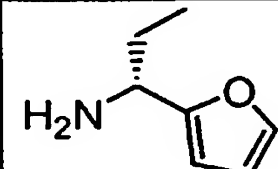
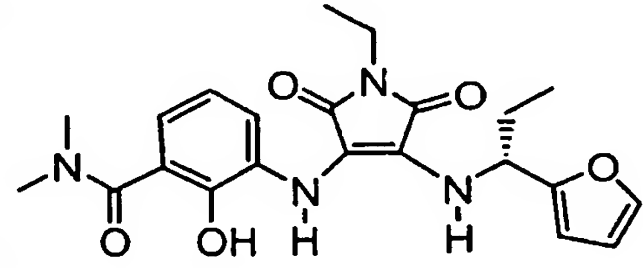
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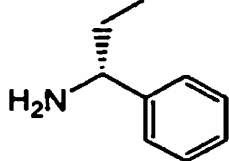
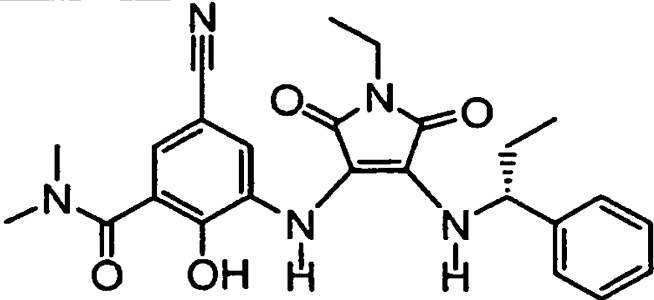
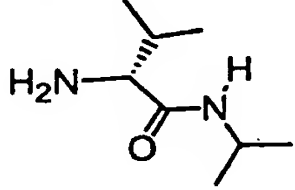
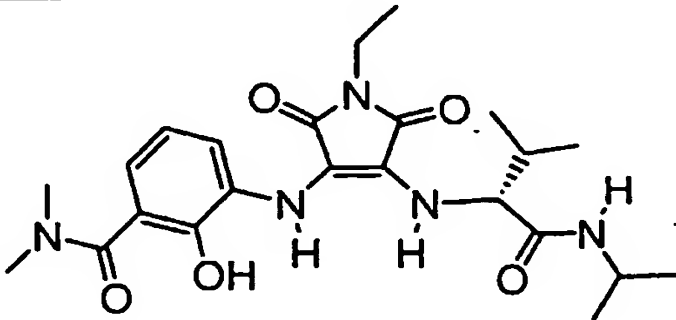
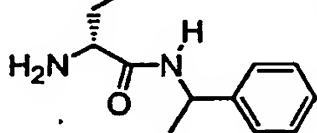
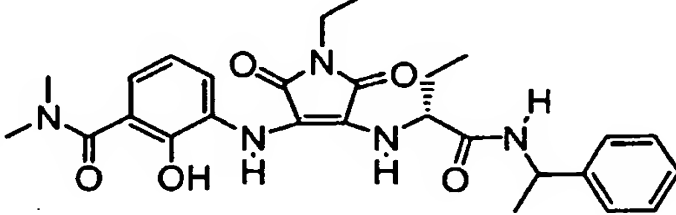
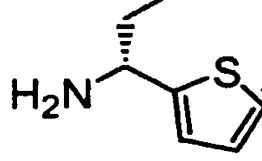
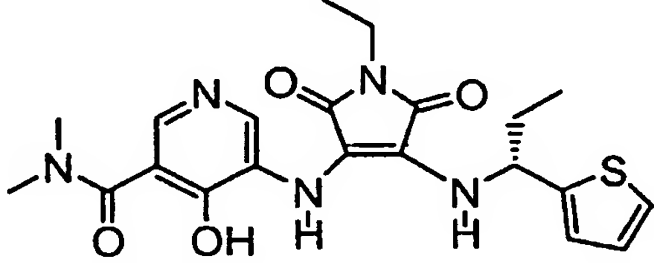
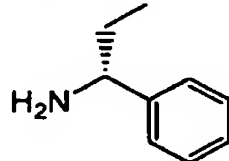
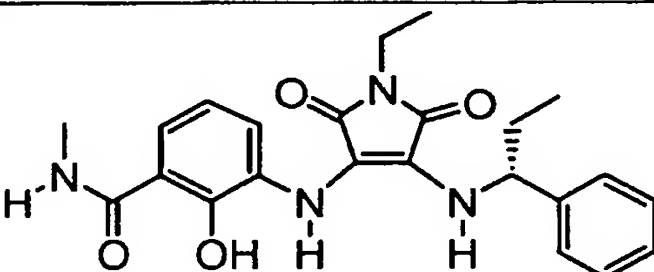
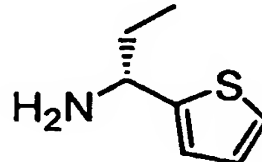
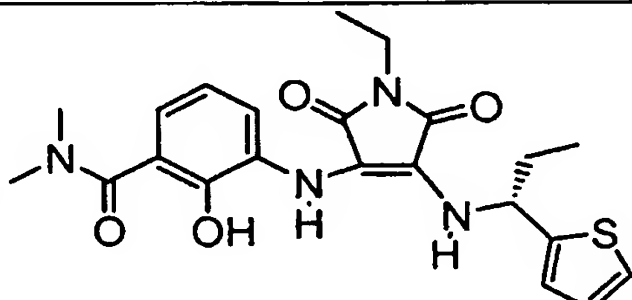
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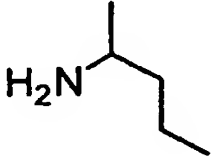
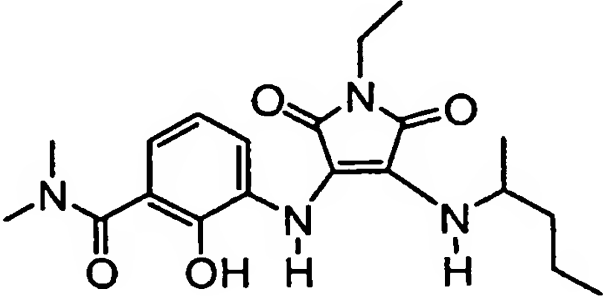
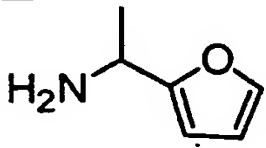
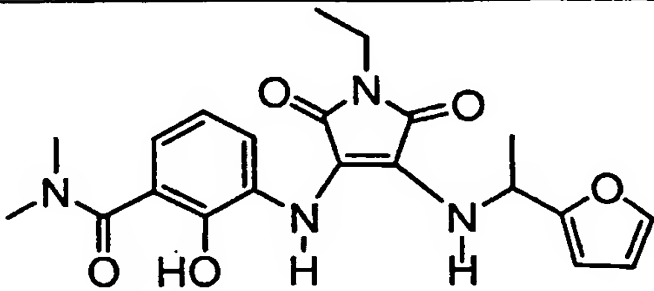
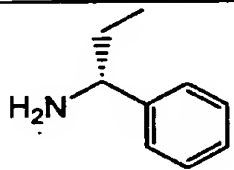
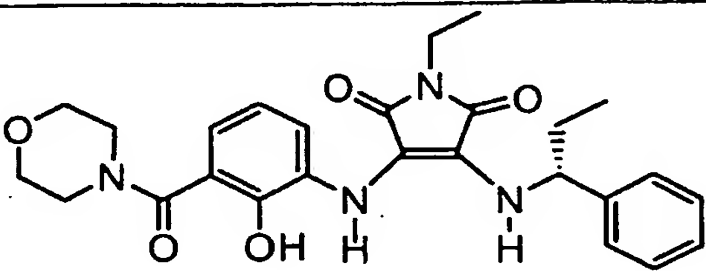
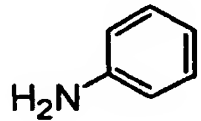
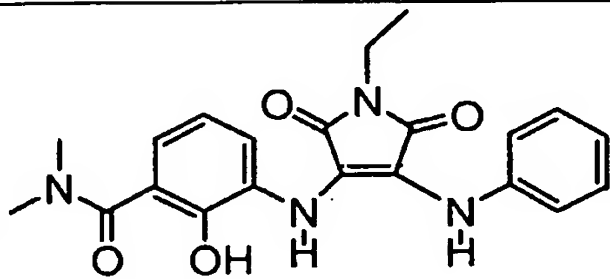
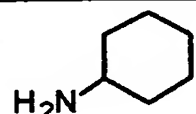
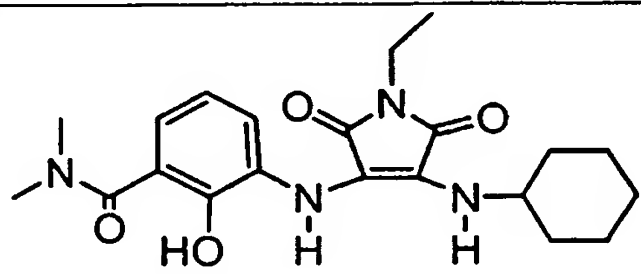
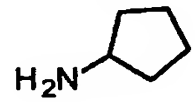
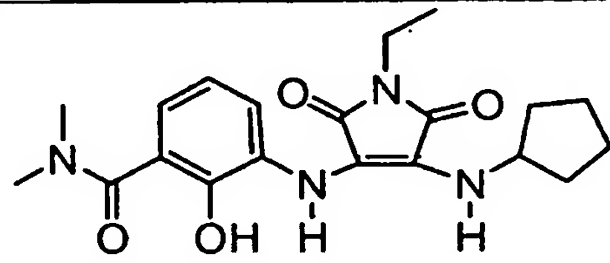
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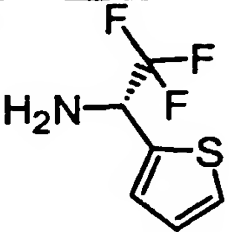
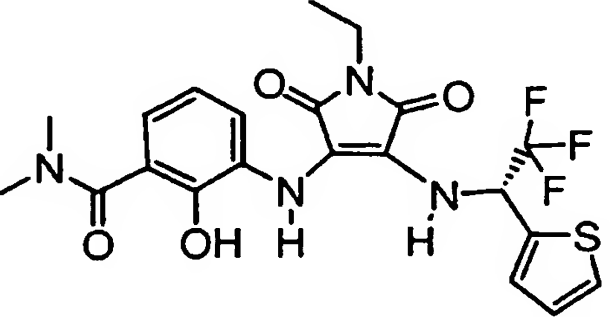
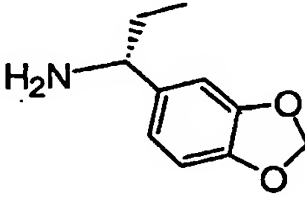
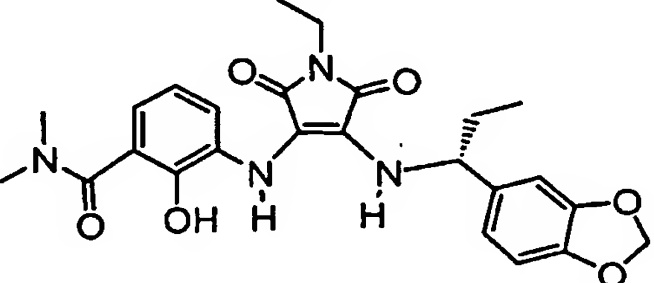
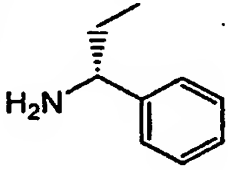
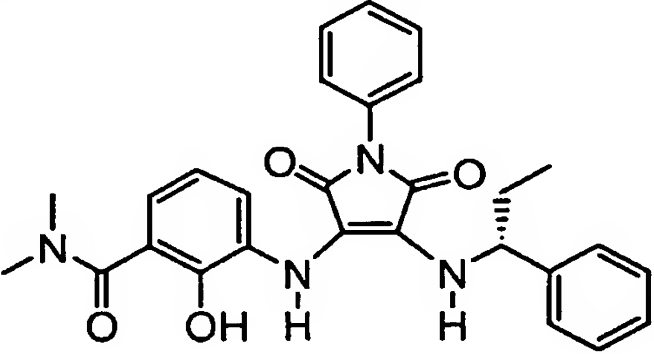
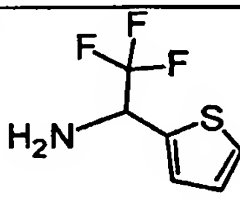
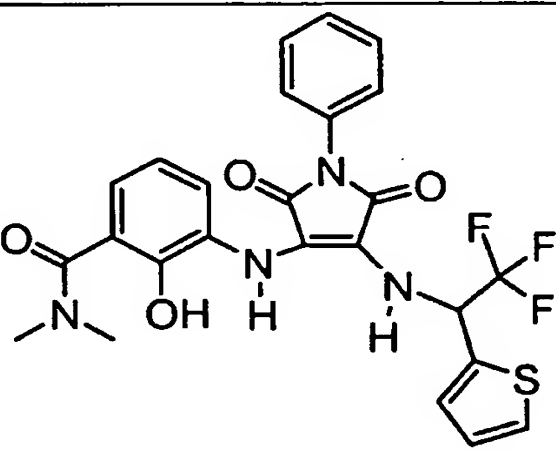
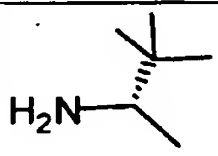
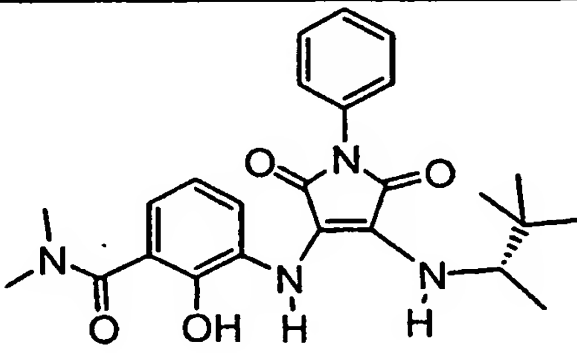
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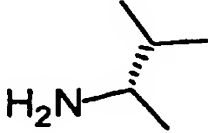
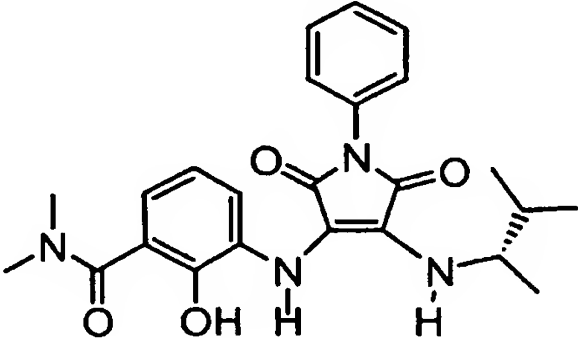
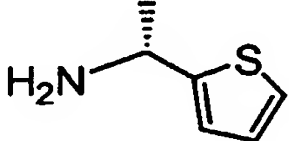
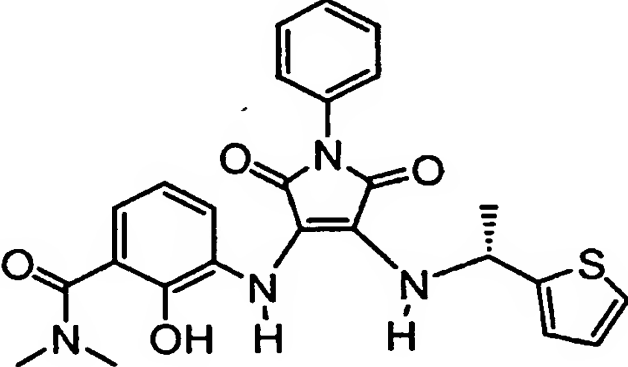
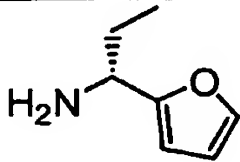
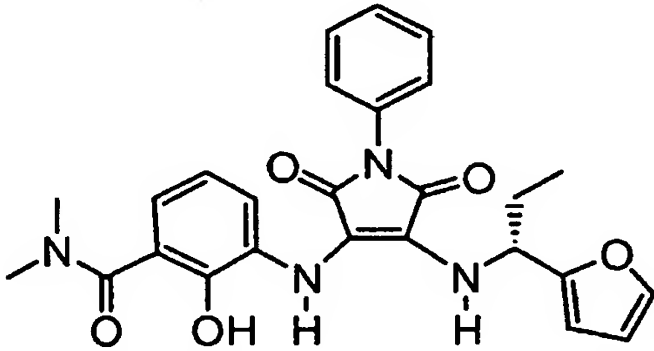
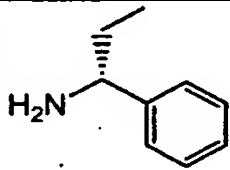
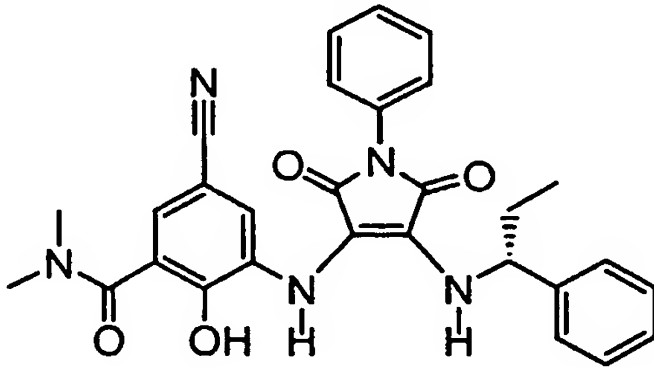
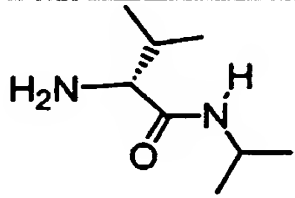
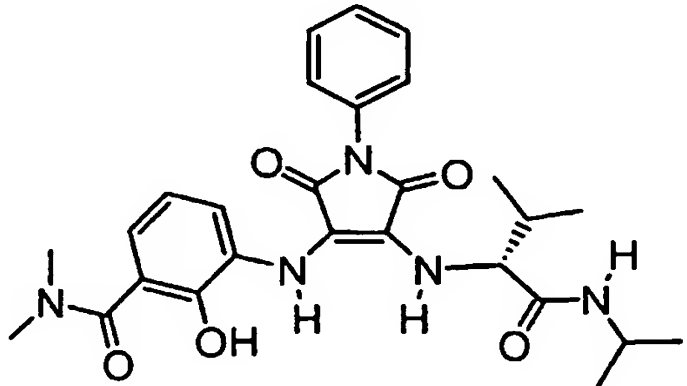
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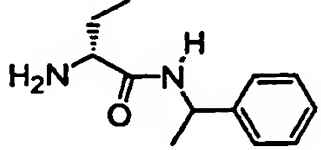
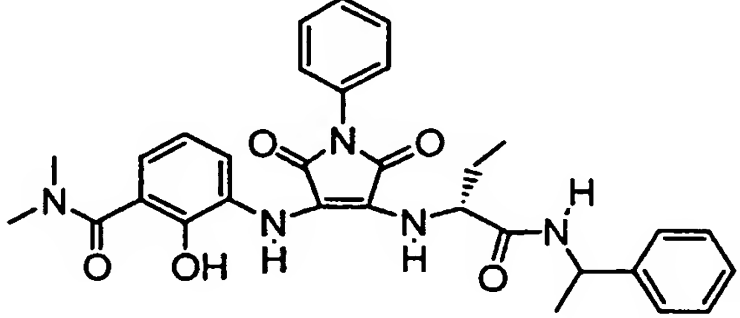
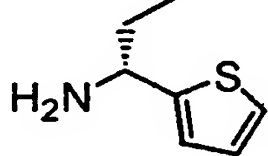
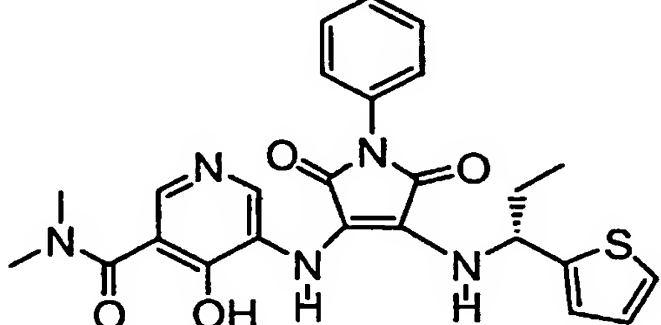
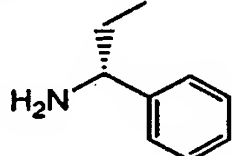
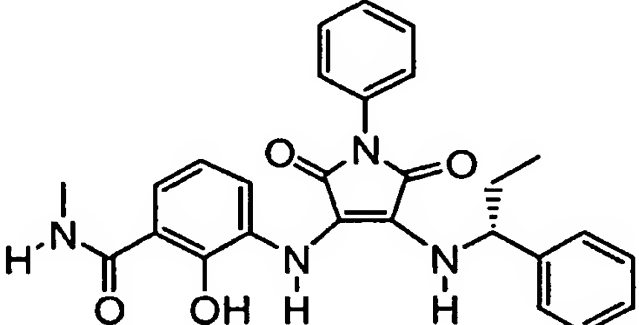
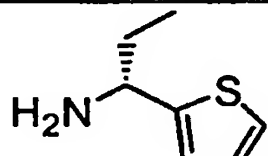
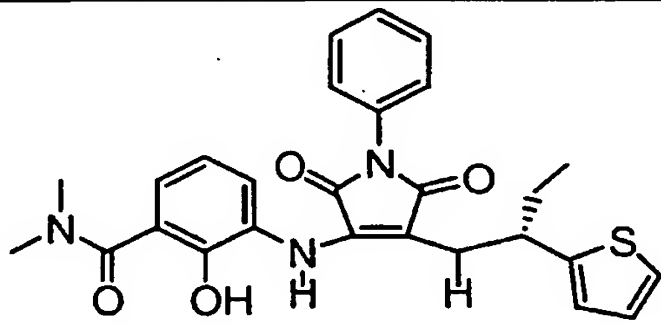
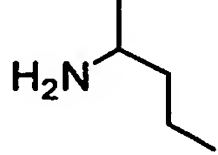
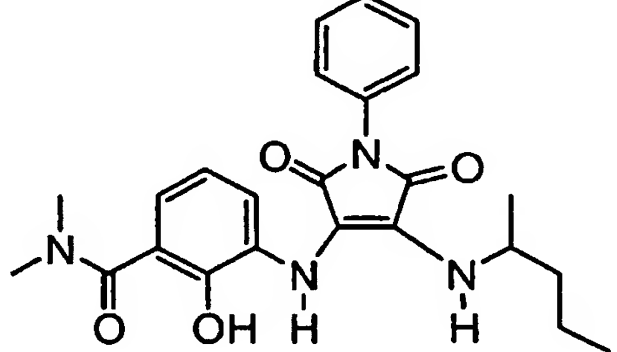
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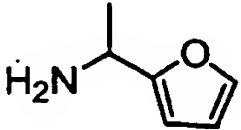
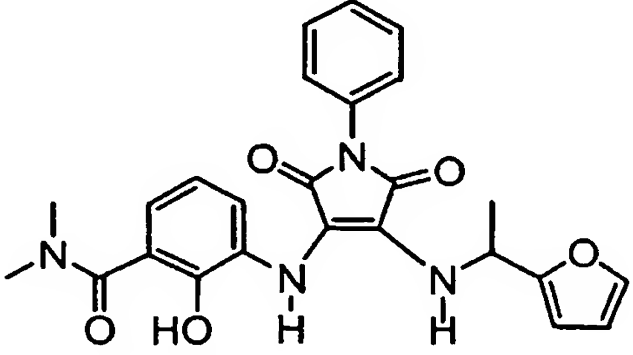
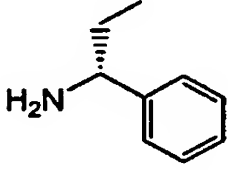
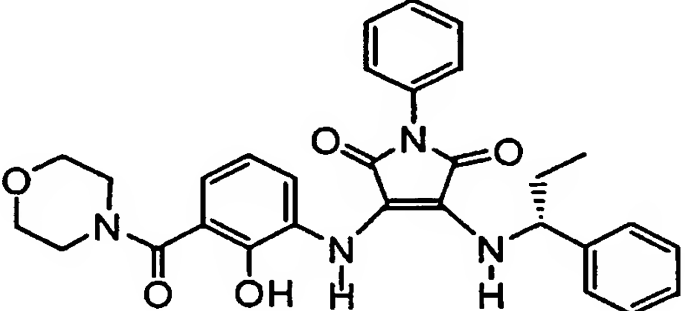
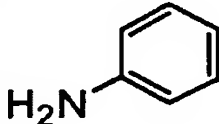
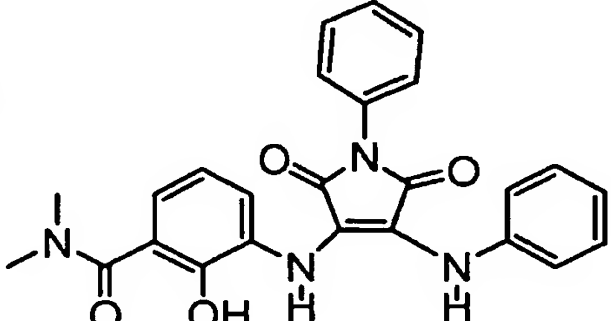
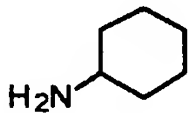
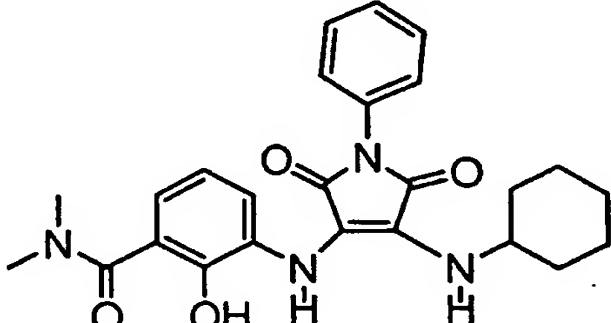
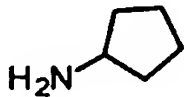
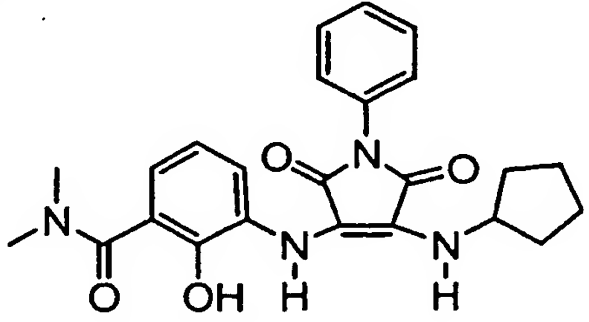
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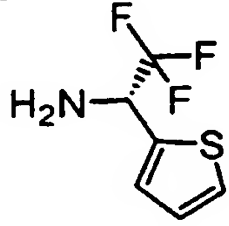
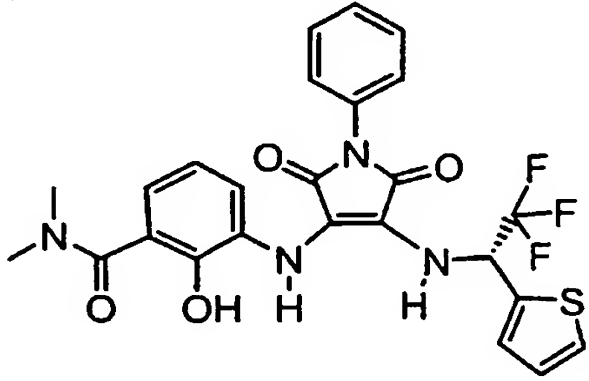
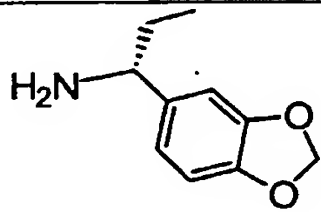
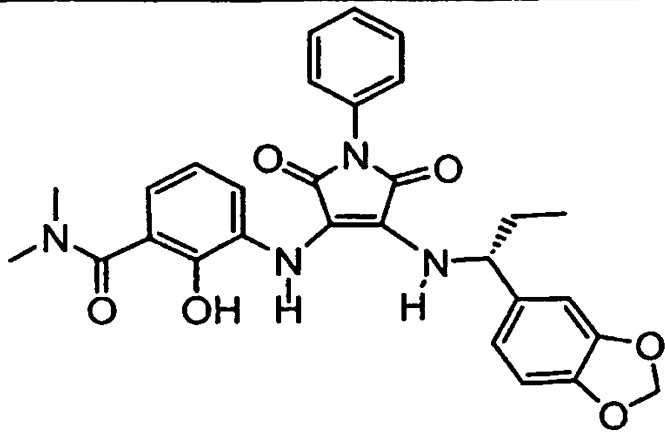
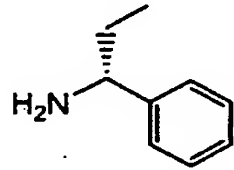
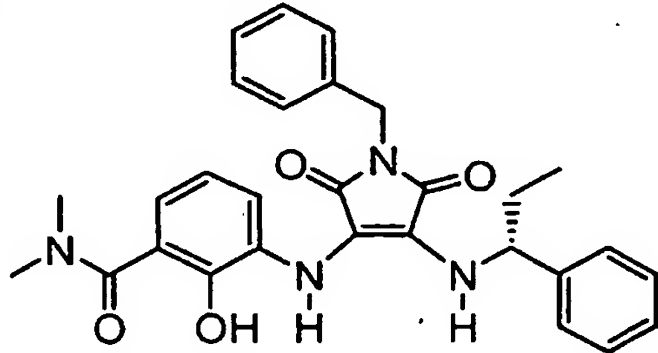
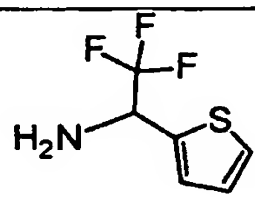
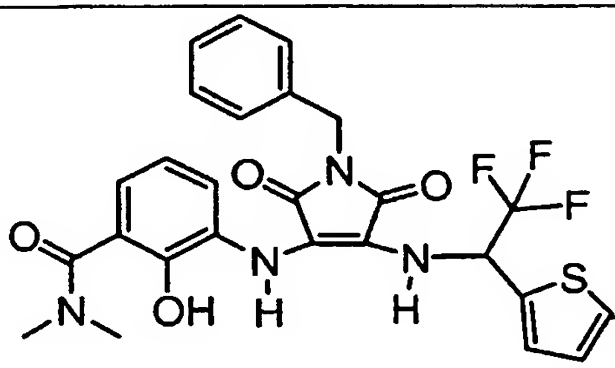
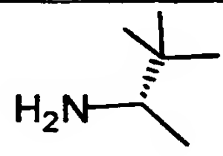
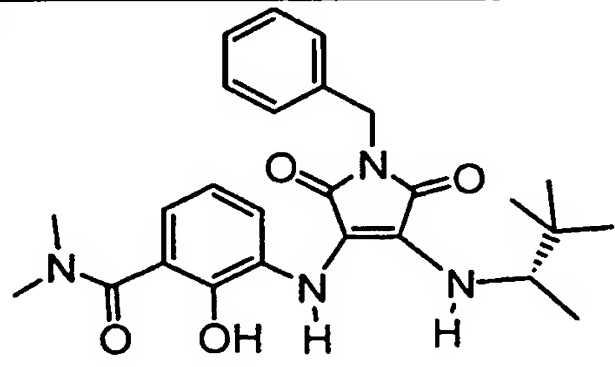
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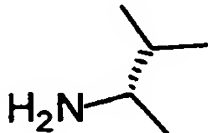
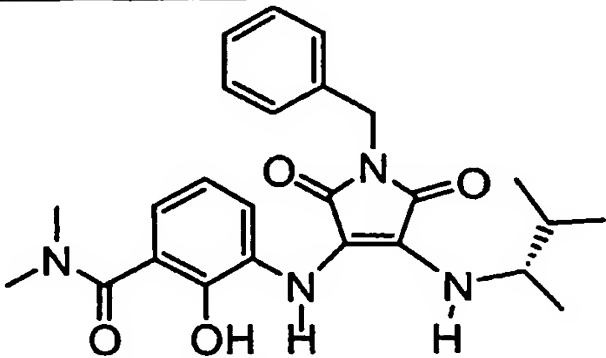
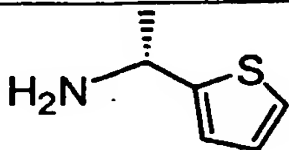
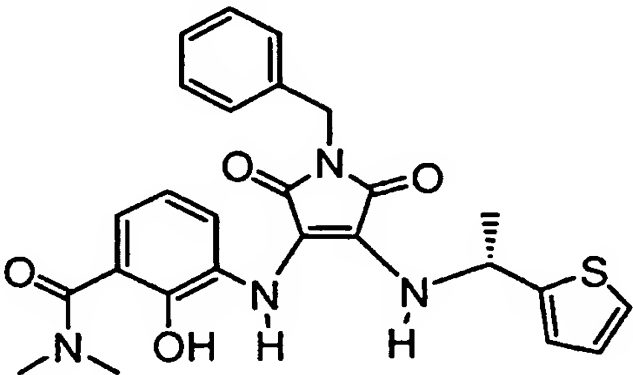
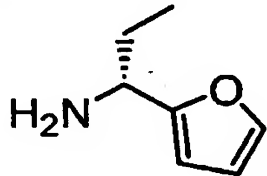
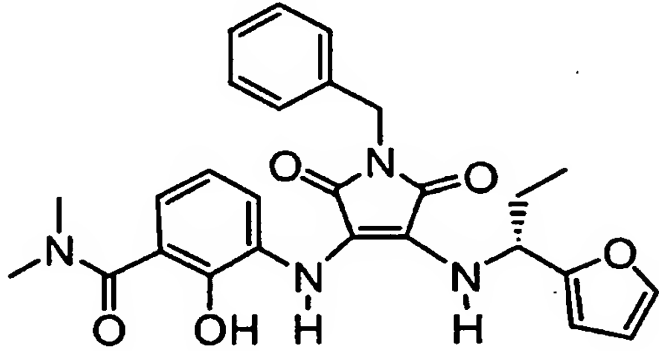
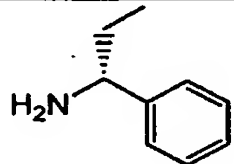
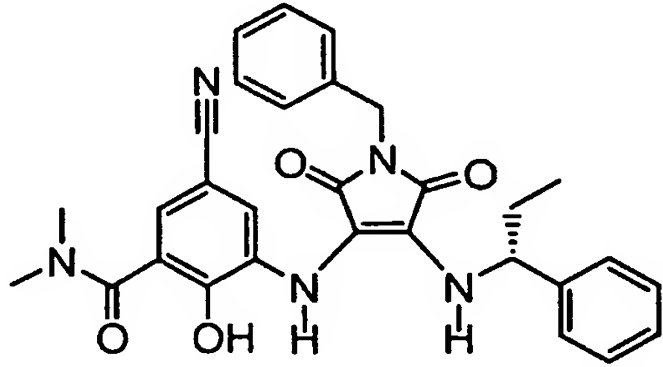
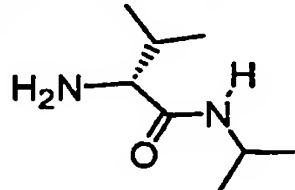
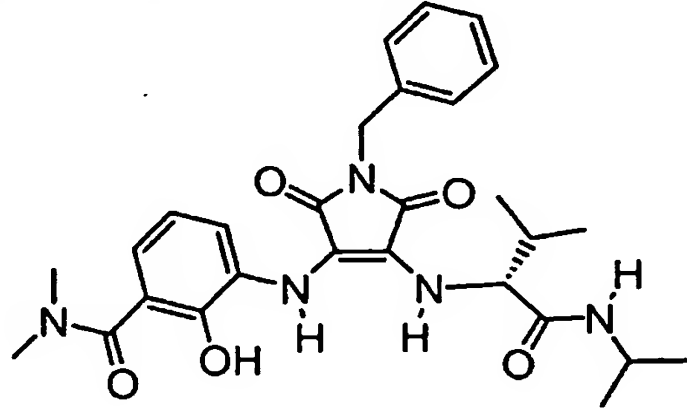
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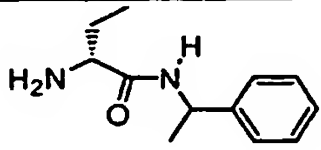
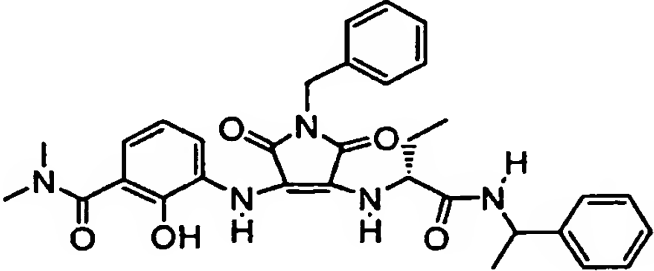
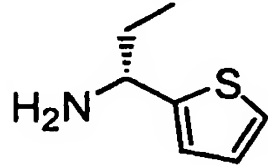
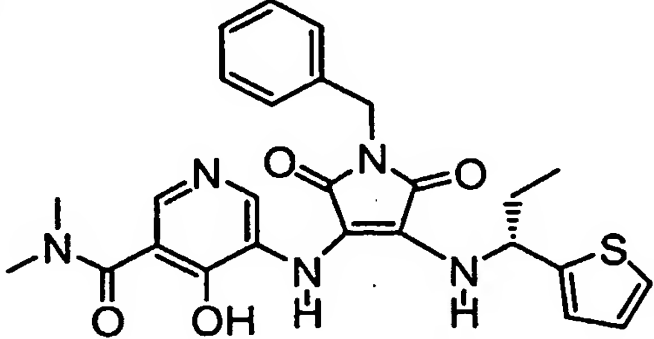
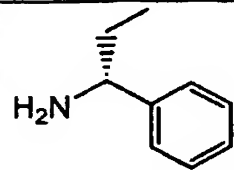
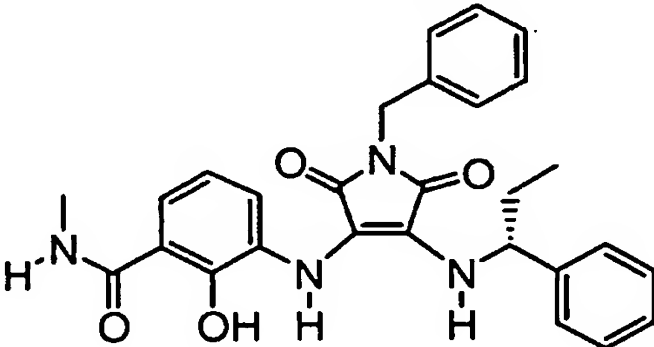
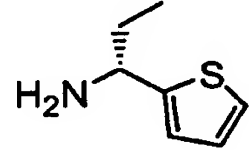
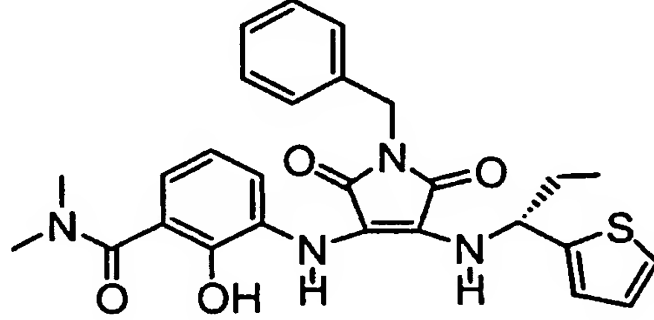
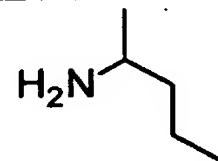
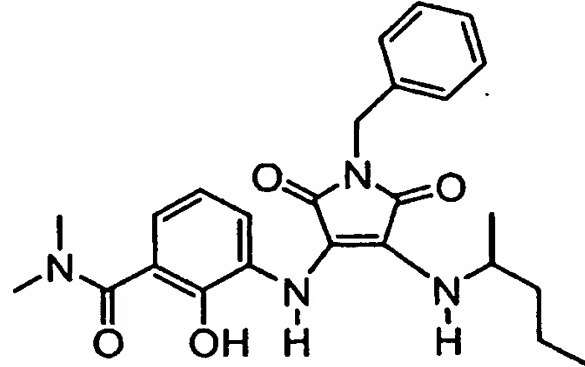
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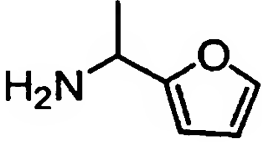
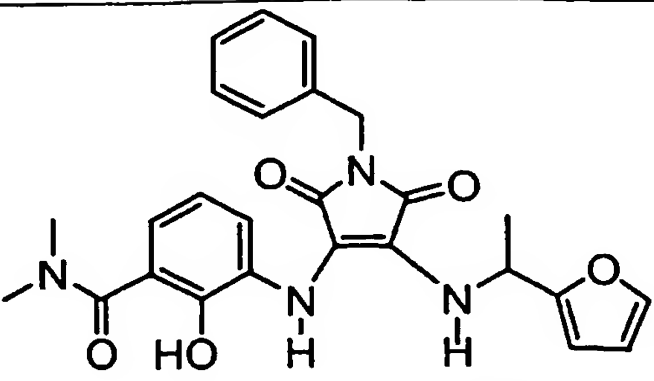
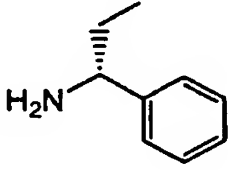
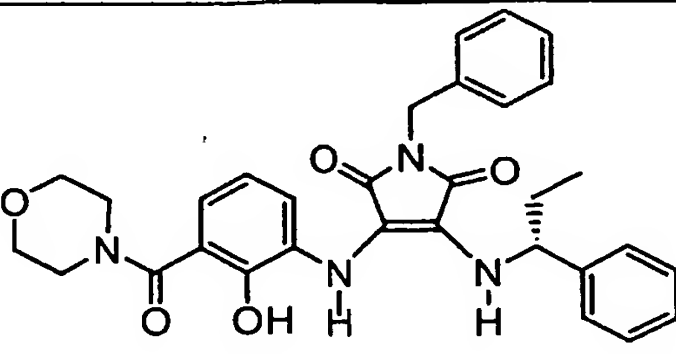
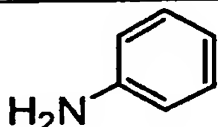
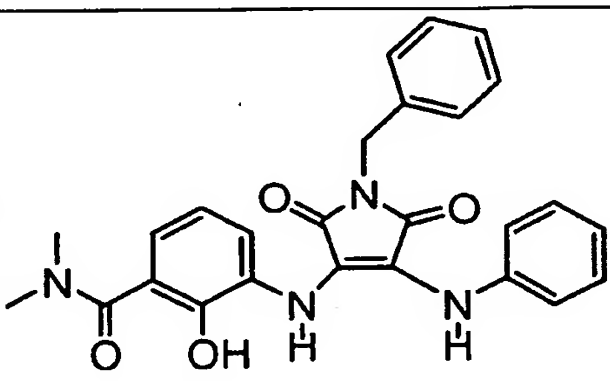
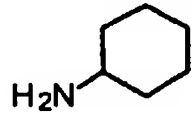
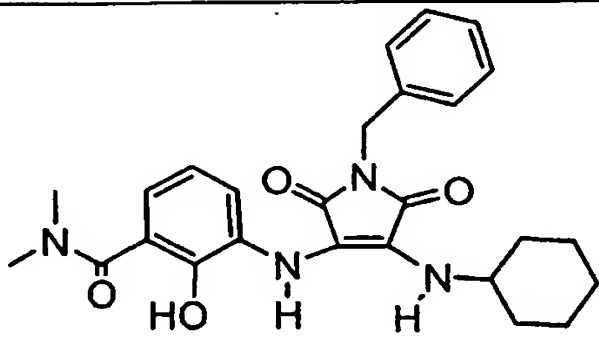
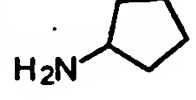
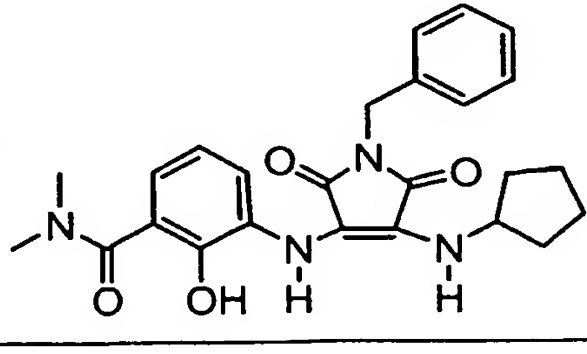
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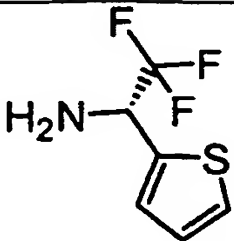
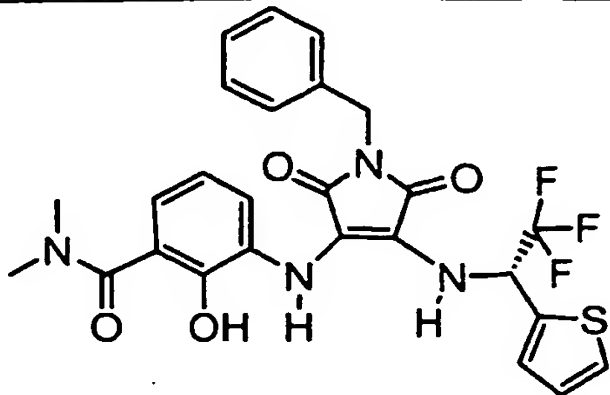
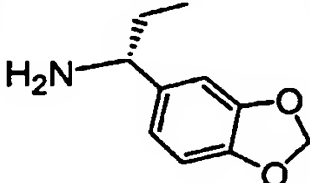
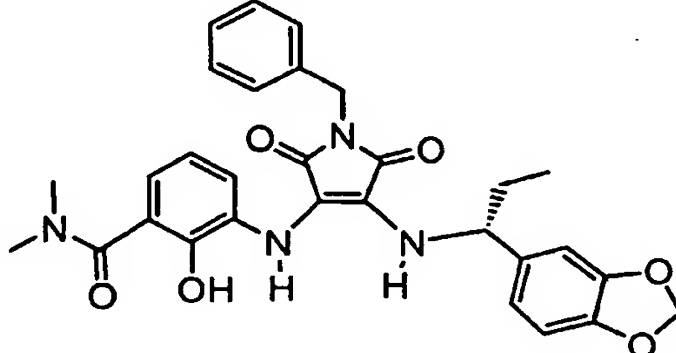
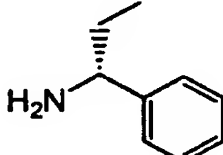
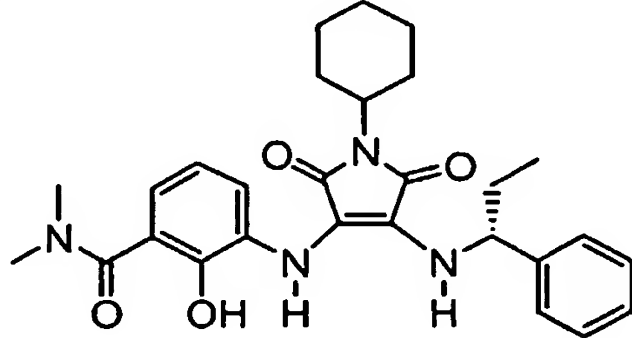
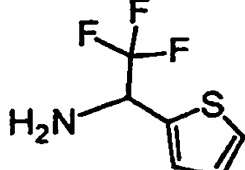
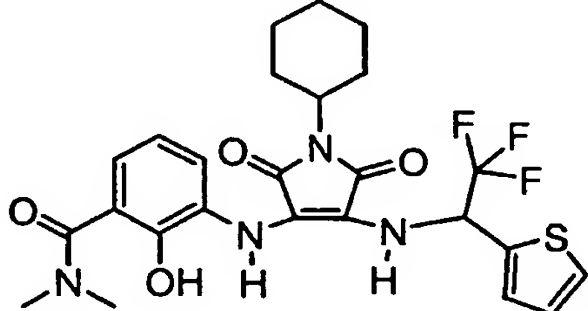
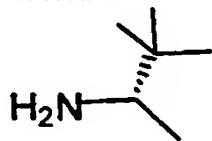
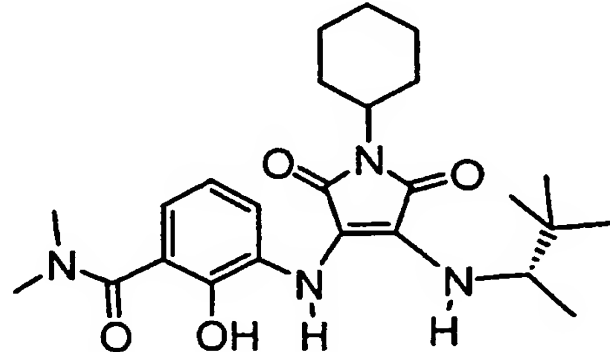
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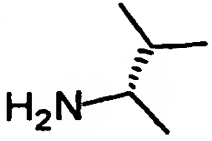
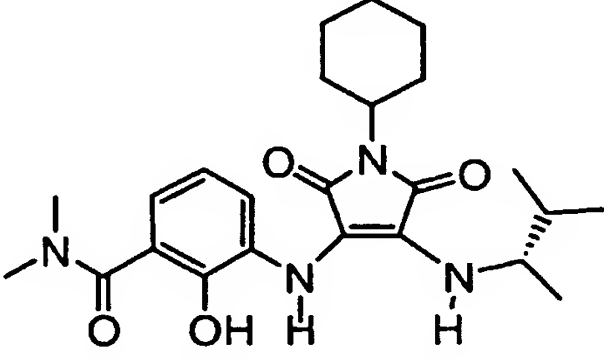
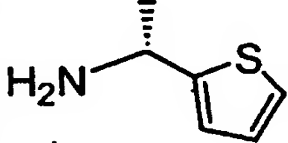
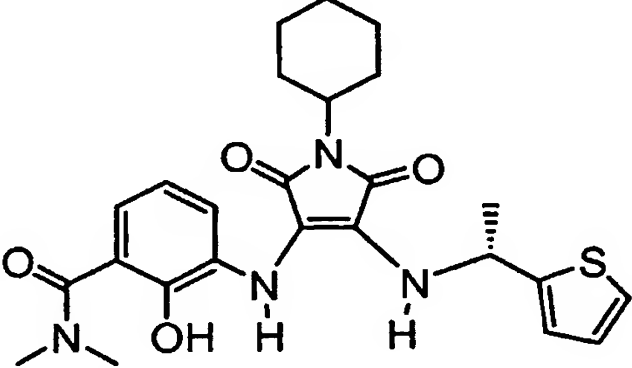
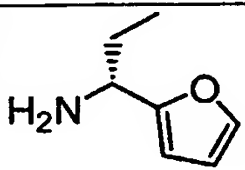
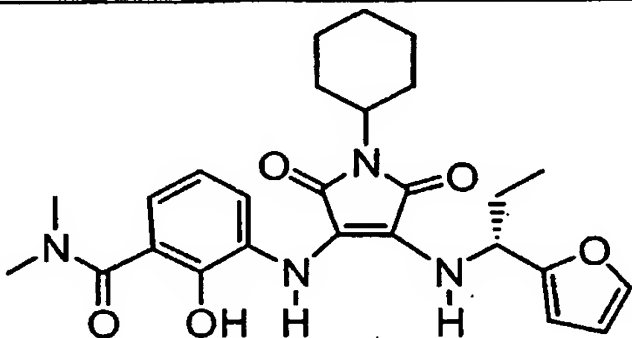
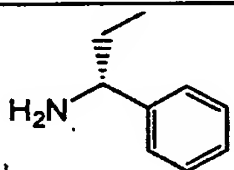
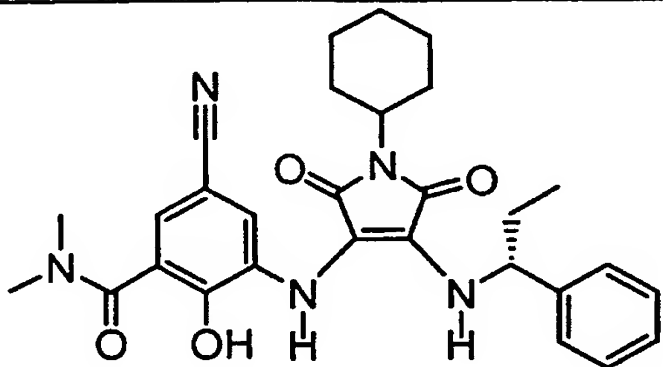
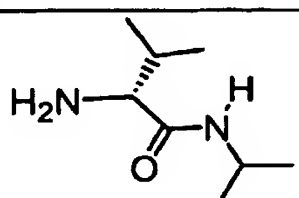
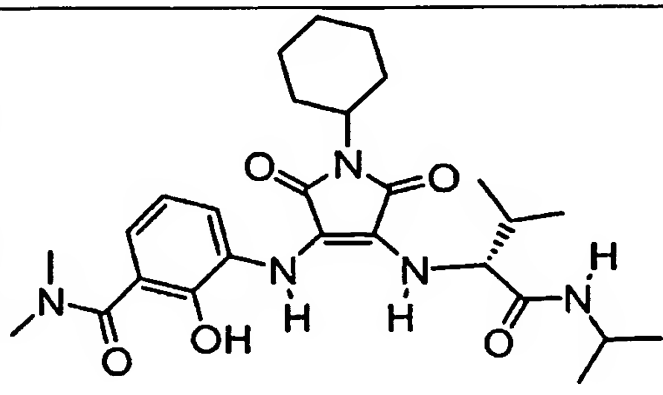
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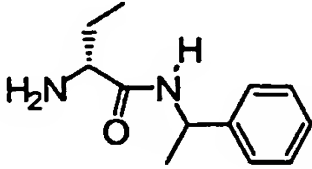
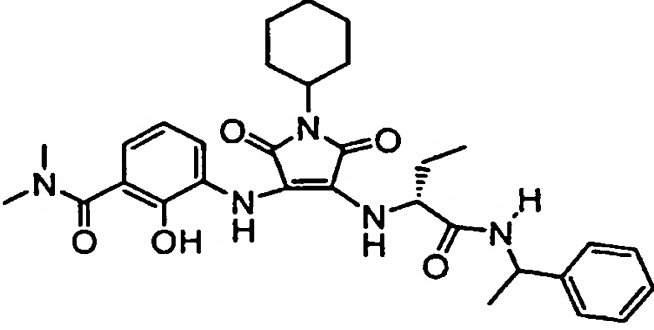
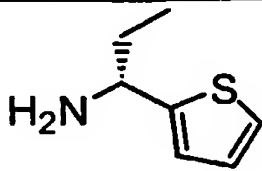
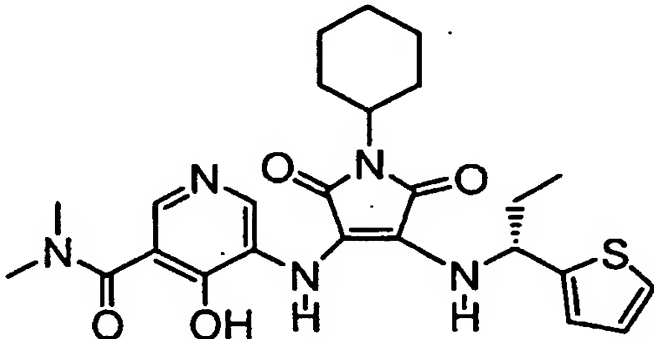
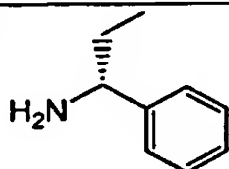
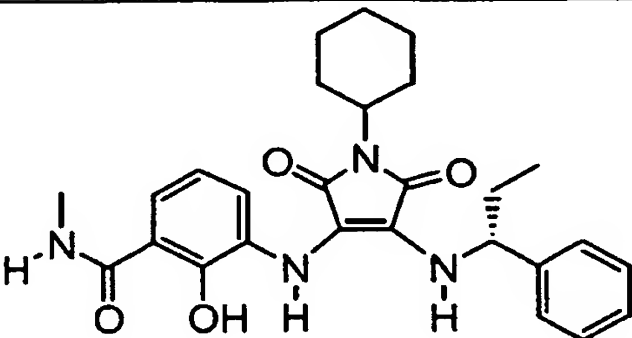
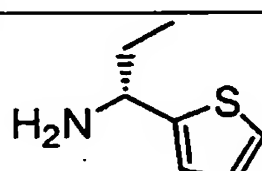
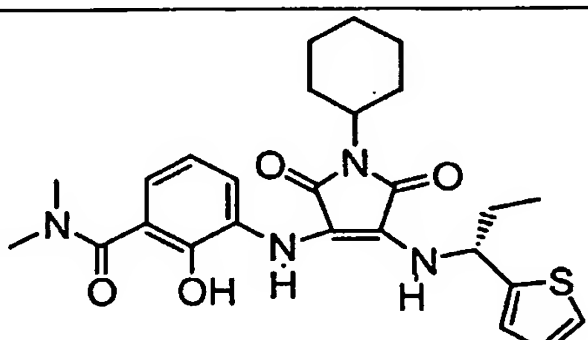
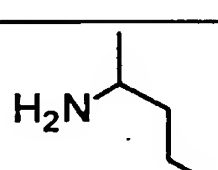
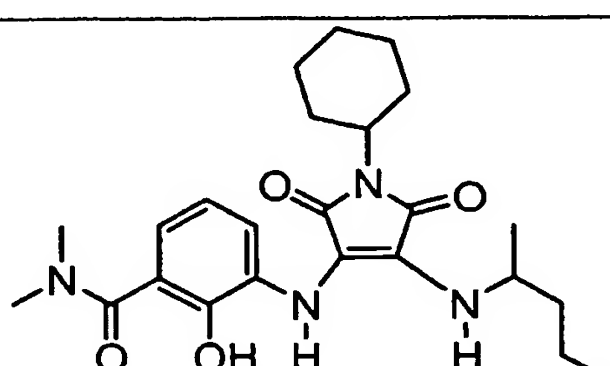
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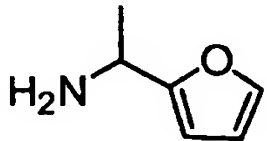
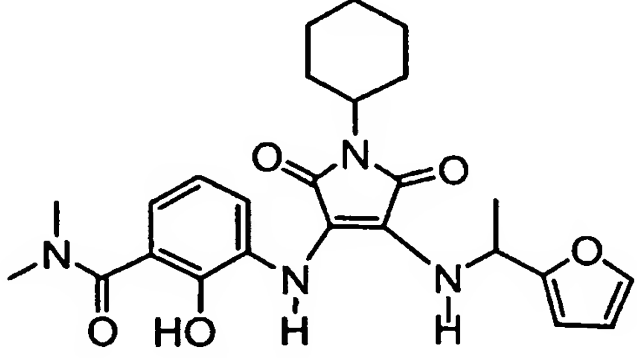
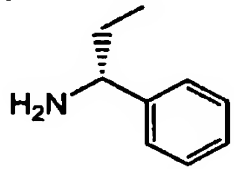
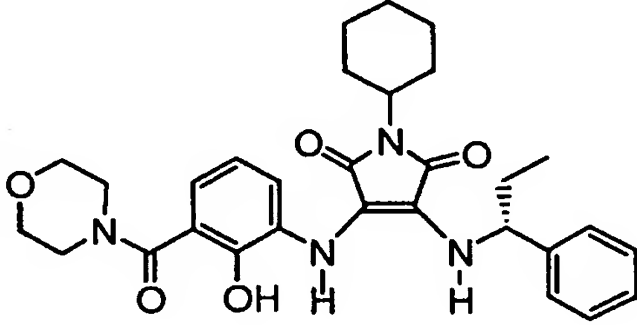
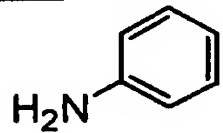
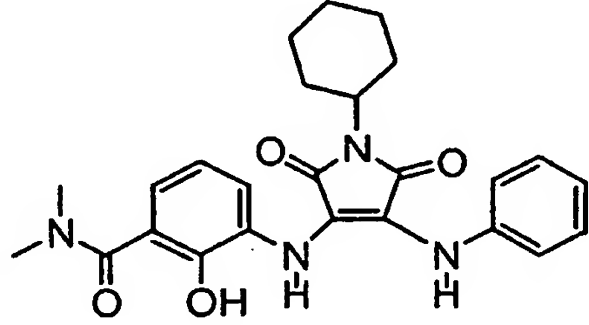
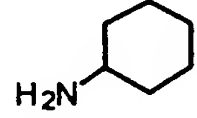
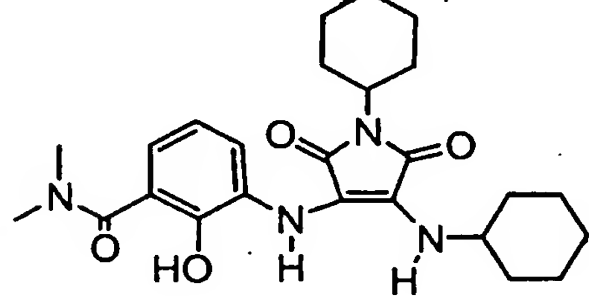
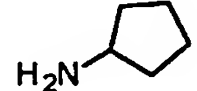
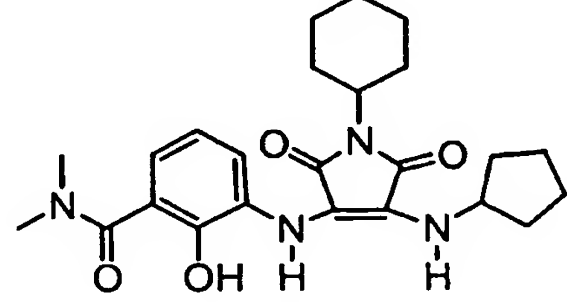
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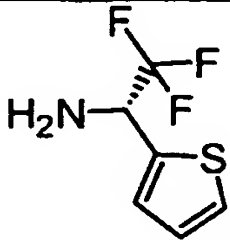
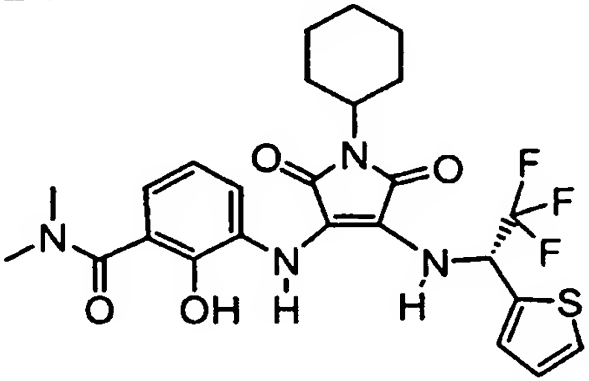
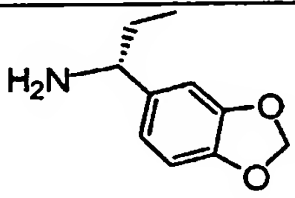
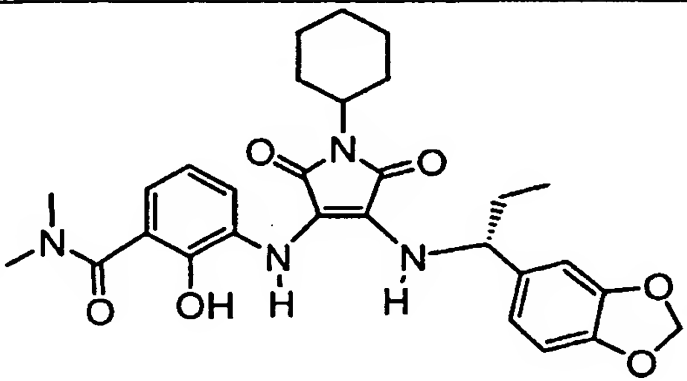
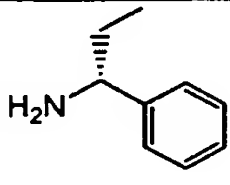
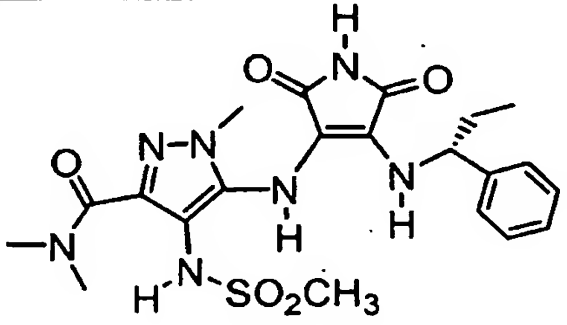
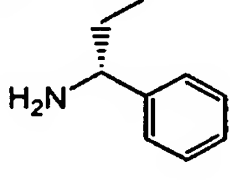
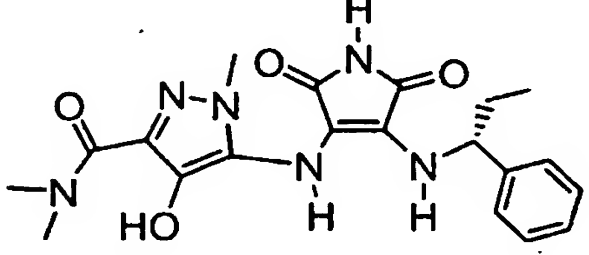
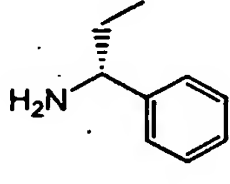
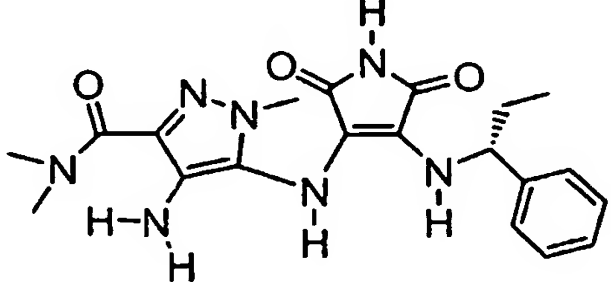
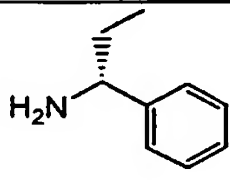
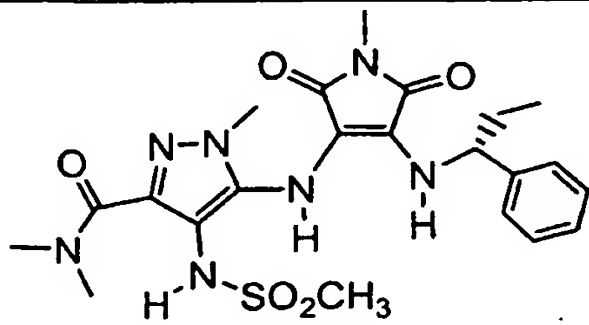
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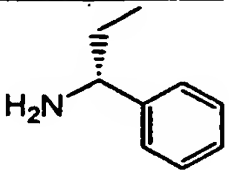
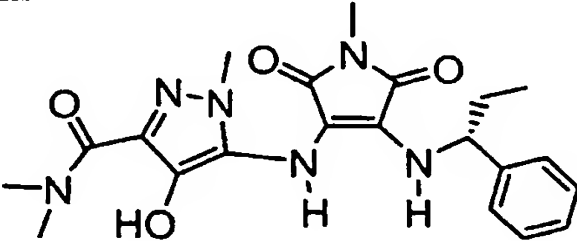
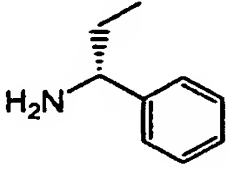
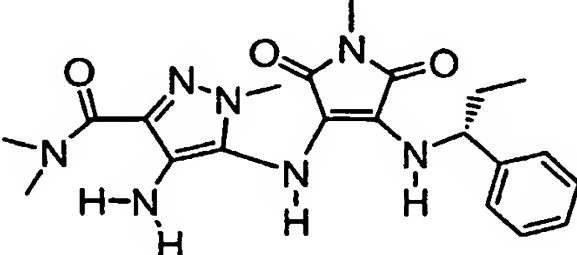
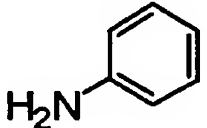
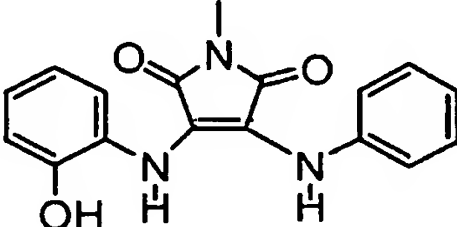
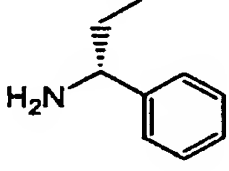
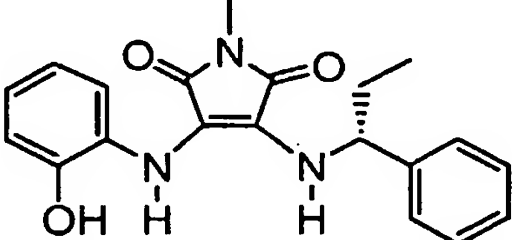
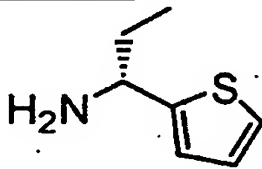
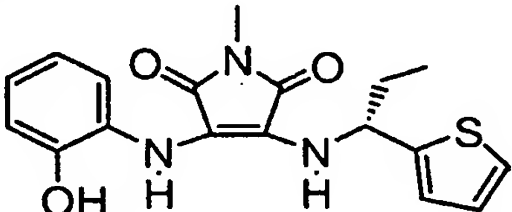
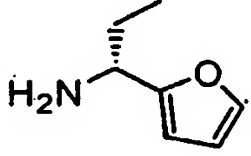
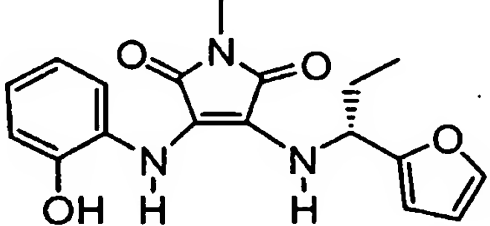
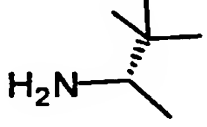
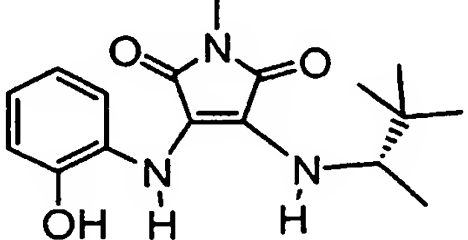
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663	 <chem>NC[C@@H]1C=CC2=CC=CC=C2O1</chem>	106	 <chem>CN(C)C(=O)c1cc(O)c(NC2=C(NC3C[C@@H](C)C4=CC=CC=C4O3)C(=O)N2Cc5ccccc5)c1</chem>
664	 <chem>NC[C@@H](c1ccccc1)C2=CC=CC=C2</chem>	96	 <chem>CN(C)C(=O)c1cc(O)c(NC2=C(NC3C[C@@H](c4ccccc4)C5=CC=CC=C5)C(=O)N2C6CCCCC6)c1</chem>
665	 <chem>NC(C(F)(F)F)c1ccsc1</chem>	96	 <chem>CN(C)C(=O)c1cc(O)c(NC2=C(NC3C(C(F)(F)F)C4=CC=CC=C4S3)C(=O)N2C5CCCCC5)c1</chem>
667	 <chem>NC(C)(C)C[C@@H]1C=CC2=CC=CC=C2O1</chem>	96	 <chem>CN(C)C(=O)c1cc(O)c(NC2=C(NC3C(C)(C)C[C@@H](C)C4=CC=CC=C4O3)C(=O)N2C5CCCCC5)c1</chem>

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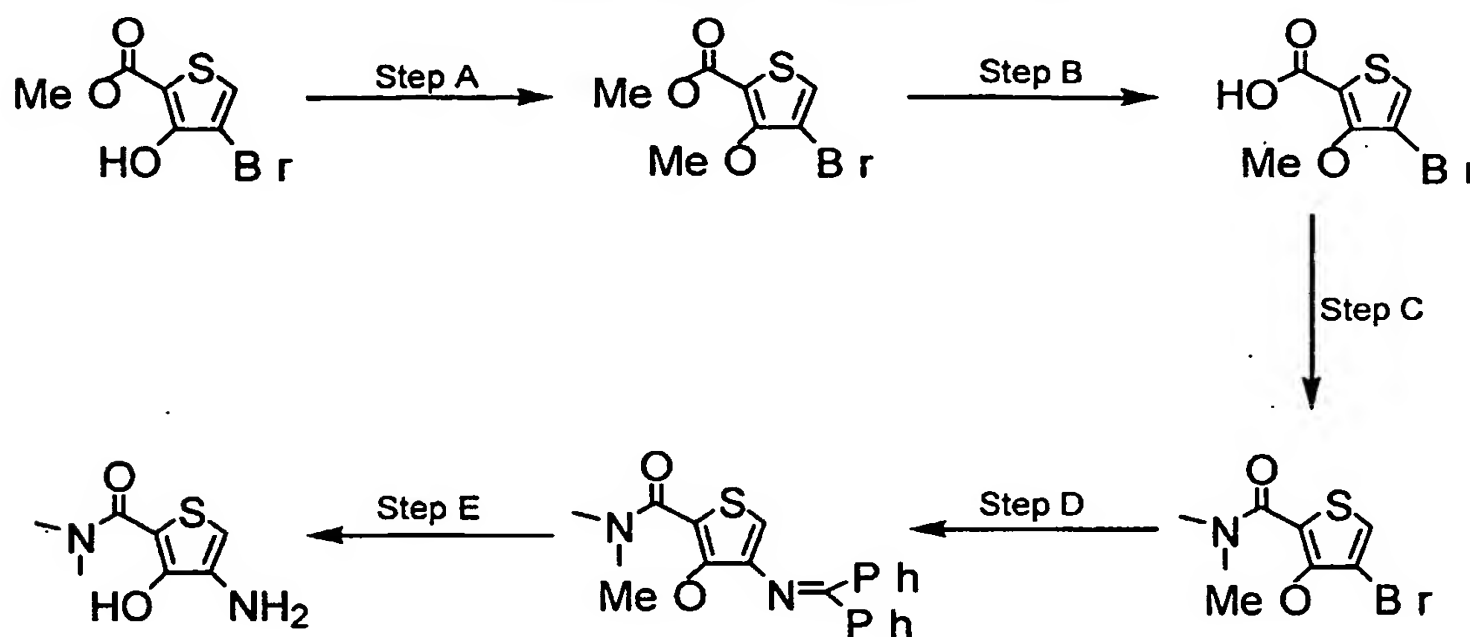
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696		111	

697		111	
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PREPARATIVE EXAMPLE 400

5 Step A

Methyl-3-hydroxy-4-bromo-2-thiophenecarboxylate (10.0 g, 42.2 mmol) was dissolved in 250 mL of acetone. Potassium carbonate (30.0 g, 217.4 mmol) was added followed by a solution of iodomethane (14.5 mL, 233.0 mmol). The mixture was heated to reflux and continued for 6 h. After cooled to room temperature, the mixture was filtered, the solid material was rinsed with acetone (~200 mL). The filtrate and rinsing were concentrated under reduced pressure to a solid, further dried on high vacuum, yielding 13.7 g (100%) of methyl-3-methoxy-4-bromo-2-thiophenecarboxylate ($MH^+ = 251.0$).

15 Step B

Methyl-3-methoxy-4-bromo-2-thiophenecarboxylate (13.7 g), available from step A, was dissolved in 75 mL of THF, and added with a 1.0 M sodium hydroxide aqueous solution (65 mL, 65.0 mmol). The mixture was stirred at room temperature for 24 h. A 1.0 M hydrogen chloride aqueous solution was added dropwise to the mixture until pH was approximately 2. The acidic mixture was extracted with CH_2Cl_2 (100 mL x 2, 50 mL). The combined organic extracts were washed with

brine (40 mL), dried with Na₂SO₄, and concentrated under reduced pressure to a solid, 10.0 g (100%, over two steps) of 3-methoxy-4-bromo-2-thiophenecarboxylic acid (MH⁺ = 237.0).

5 Step C

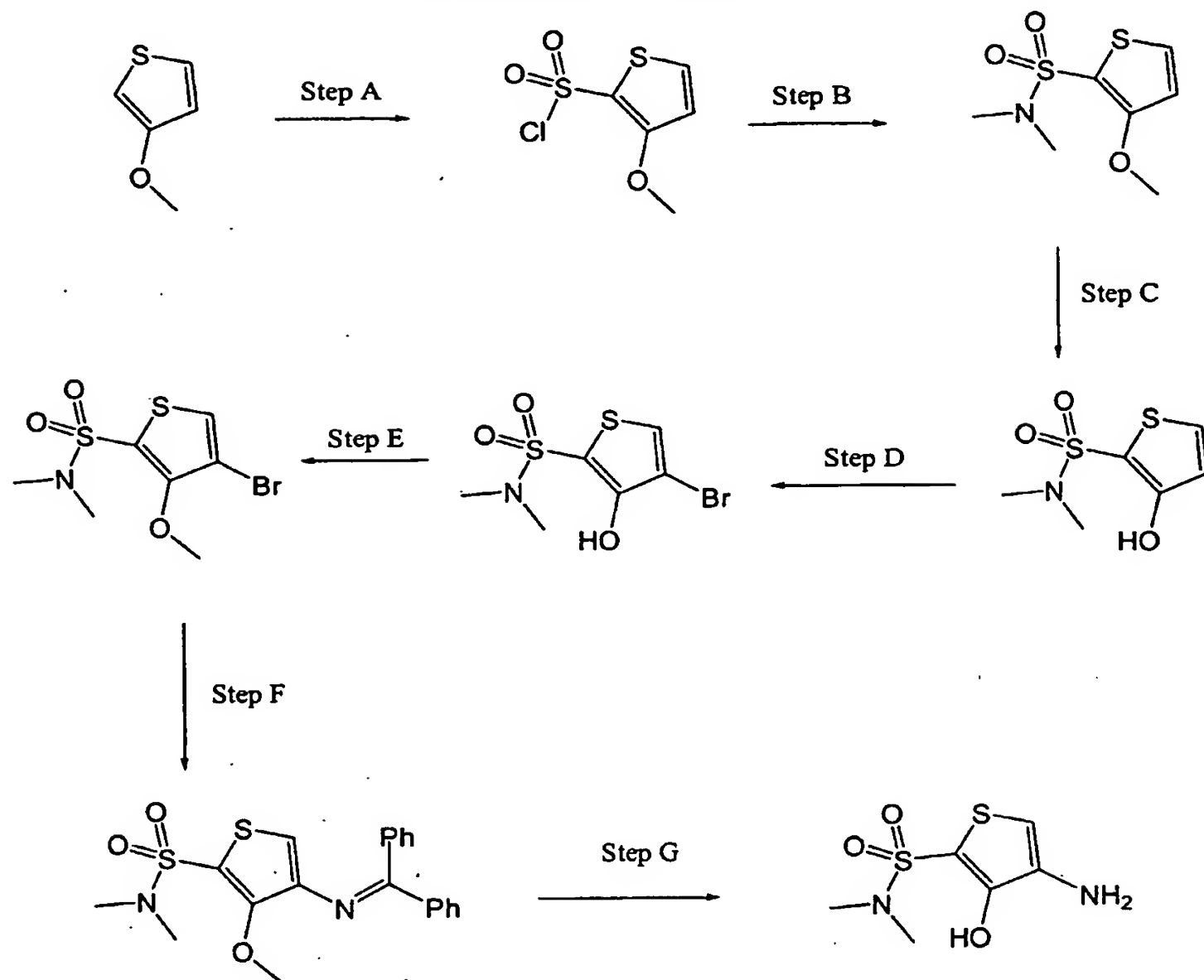
To a stirred solution of 3-methoxy-4-bromo-2-thiophenecarboxylic acid (6.5 g, 27.4 mmol) in 140 mL of CH₂Cl₂, obtained from step B, was added bromotripyrrolidinophosphonium hexafluorophosphate (PyBrop, 12.8 g, 27.5 mmol), a 2.0 M solution of dimethyl amine in THF (34.5 mL, 69.0 mmol), and diisopropylethyl
10 amine (12.0 mL; 68.7 mmol). After 3 d, the mixture was diluted with 100 mL of CH₂Cl₂, and washed with a 1.0 M sodium hydroxide aqueous solution (30 mL x 3) and brine (30 mL). The organic solution was dried with Na₂SO₄, filtered, and concentrated to an oil. This crude oil product was purified by flash column chromatography, eluting with CH₂Cl₂-hexanes (1:1, v/v). Removal of solvents
15 afforded a solid, further dried on high vacuum, yielding 6.76 g (93 %) of *N, N'*-dimethyl-3-methoxy-4-bromo-2-thiophenecarboxamide (MH⁺ = 265.0, M+2 = 266.1).

Step D

An oven dried three-neck round bottom flask was equipped with a refluxing
20 condenser, charged sequentially with palladium acetate (95 mg, 0.42 mmol), (*R*)-BINAP (353 mg, 0.57 mmol), cesium carbonate (9.2 g, 28.33 mmol), and *N, N'*-dimethyl-3-methoxy-4-bromo-2-thiophenecarboxamide (3.74 g, 14.2 mmol, from Step C). The solid mixture was flushed with nitrogen. Toluene (95 mL) was added to the solid mixture followed by benzophenone imine (3.6 mL, 21.5 mmol). The
25 mixture was heated to reflux and continued for 10 h. A second batch of palladium acetate (95 mg, 0.42 mmol) and (*R*)-BINAP (353 mg, 0.57 mmol) in 5 mL of toluene was added. Refluxing was continued for 14 h. The third batch of palladium acetate (30 mg, 0.13 mmol) and (*R*)-BINAP (88 mg, 0.14 mmol) was added, and reaction continued at 110°C for 24 h. The mixture was cooled to room temperature, diluted
30 with ether (50 mL), filtered through a layer of Celite, rinsing with ether. The filtrate and rinsing were concentrated under reduced pressure to an oil, which was purified twice by flash column chromatography using CH₂Cl₂ and CH₂Cl₂-MeOH (200:1) as eluents. Removal of solvents afforded 4.1 g (79 %) of the amido-thiophene diphenylimine product as a solid (MH⁺ = 365.1).

Step E

To a stirred solution of thiophene imine (5.09 g, 13.97 mmol), obtained from step D, in 140 mL of CH₂Cl₂ at -78°C was added dropwise a 1.0 M solution of boron tribromide in CH₂Cl₂. The mixture was stirred for 3 h while the temperature of the cooling bath was increased slowly from -78°C to -15°C. 100 mL of H₂O was added, the mixture was stirred at room temperature for 30 min, then the two layers were separated. The organic layer (as A) was extracted with H₂O (30 mL x 2). The aqueous layer and aqueous extracts were combined, washed with CH₂Cl₂ (30 mL), and adjusted to pH ~ 8 using a saturated NaHCO₃ aqueous solution. The neutralized aqueous solution was extracted with CH₂Cl₂ (100 mL x 3), the extracts were washed with brine, dried with Na₂SO₄, and concentrated under reduced pressure to a light yellow solid, 1.49 g of *N, N'*-dimethyl-3-hydroxy-4-amino-2-thiophenecarboxamide (first crop). The previous separated organic layer A and organic washing were combined, stirred with 30 mL of a 1.0 M HCl aqueous solution for 1 h. The two layers were separated, the aqueous layer was washed with CH₂Cl₂ (30 mL) and adjusted to pH ~8 using a saturated NaHCO₃ aqueous solution, and the separated organic layer and organic washing were combined as organic layer B. The neutralized aqueous solution was extracted with CH₂Cl₂ (30 mL x 4), the extracts were washed with brine, dried by Na₂SO₄, and concentrated under reduced pressure to give 0.48g of a solid as the second crop of the titled product. Organic layer B from above was washed with brine, and concentrated to an oil, which was separated by preparative TLC (CH₂Cl₂-MeOH = 50:1) to afford 0.45 g of a solid as the third crop of the titled product. The overall yield of the product, *N, N'*-dimethyl-3-hydroxy-4-amino-2-thiophenecarboxamide, is 2.32 g (89%) (MH⁺ = 187.0).

156
PREPARATIVE EXAMPLE 401Step A

To a solution of 3-methoxythiophene (3 g) in dichloromethane (175 mL) at
5 -78°C was added chlorosulfonic acid (8.5 mL) dropwise. The mixture was stirred
for 15 min at -78°C and 1.5 h at room temp. Afterwards, the mixture was poured
carefully into crushed ice, and extracted with dichloromethane. The extracts were
washed with brine, dried over magnesium sulfate, filtered through a 1-in silica gel
pad. The filtrate was concentrated in vacuo to give the desired compound (4.2 g).

Step B

The product from Step A above (4.5 g) was dissolved in dichloromethane
(140 mL) and added with triethylamine (8.8 mL) followed by diethyl amine in THF
(2M, 21 mL). The resulting mixture was stirred at room temperature overnight. The
15 mixture was washed with brine and saturated bicarbonate (aq) and brine again,

dried over sodium sulfate, filtered through a 1-in silica gel pad. The filtrate was concentrated in vacuo to give the desired compound (4.4 g).

Step C

5 The product from Step B above (4.3 g) was dissolved in dichloromethane (125 mL) and cooled in a -78°C bath. A solution of boron tribromide (1.0 M in dichloromethane, 24.3 mL) was added. The mixture was stirred for 4 h while the temperature was increased slowly from -78°C to 10°C. H₂O was added, the two layers were separated, and the aqueous layer was extracted with dichloro-
10 methane. The combined organic layer and extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to give 3.96 g of the desired hydroxy-compound.

Step D

15 The product from step C above (3.96 g) was dissolved in 125 mL of dichloromethane, and added with potassium carbonate (6.6 g) followed by bromine (2 mL). The mixture was stirred for 5 h at room temperature, quenched with 100 mL of H₂O. The aqueous mixture was adjusted to pH ~ 5 using a 0.5N hydrogen chloride aqueous solution, and extracted with dichloromethane. The extracts were
20 washed with a 10 % Na₂S₂O₃ aqueous solution and brine, dried over sodium sulfate, and filtered through a celite pad. The filtrate was concentrated in vacuo to afford 4.2 g of the desired bromo-compound.

Step E

25 The product from Step D (4.2 g) was dissolved in 100 mL of acetone and added with potassium carbonate (10 g) followed by iodomethane (9 mL). The mixture was heated to reflux and continued for 3.5 h. After cooled to room temperature, the mixture was filtered through a Celite pad. The filtrate was concentrated in vacuo to a dark brown residue, which was purified by flash column
30 chromatography eluting with dichloromethane-hexanes (1:1, v/v) to give 2.7 g of the desired product.

Step F

The product from step E (2.7 g) was converted to the desired imine compound (3 g), following the similar procedure to that of Preparative Example 400 step D.

5

Step G

The imine product from step F (3 g) was dissolved in 80 mL of dichloromethane and cooled in a -78°C bath. A solution of boron tribromide (1.0 M in dichloromethane, 9.2 mL) was added dropwise. The mixture was stirred for 4.25 h from -78°C to 5°C . H_2O (50 mL) was added, and the layers were separated. The aqueous layer was extracted with dichloromethane. The organic layer and extracts were combined, washed with brine, and concentrated to an oily residue. The residue was dissolved in 80 mL of methanol, stirred with sodium acetate (1.5 g) and hydroxyamine hydrochloride (0.95 g) at room temperature for 2 h. The mixture was poured into an aqueous mixture of sodium hydroxide (1.0 M aq, 50 mL) and ether (100 mL). The two layers were separated. The aqueous layer was washed with ether three times. The combined ether washings were re-extracted with H_2O once. The aqueous layers were combined, washed once with dichloromethane, adjusted to pH ~ 6 using 3.0 M and 0.5 M hydrogen chloride aqueous solutions, and extracted with dichloromethane. The organic extracts were combined, washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 1.2 g of desired amine compound.

10

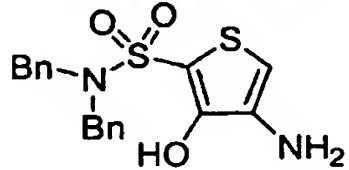
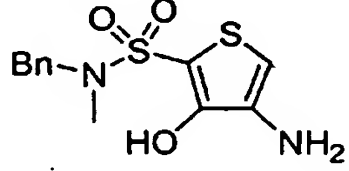
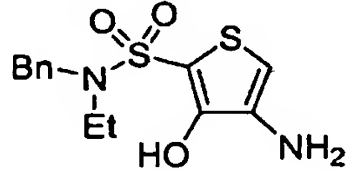
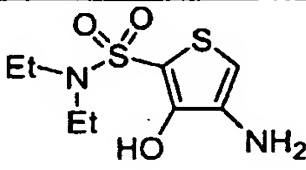
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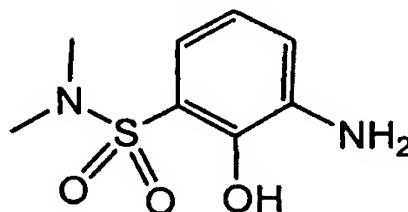
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PREPARATIVE EXAMPLES 402-405

25

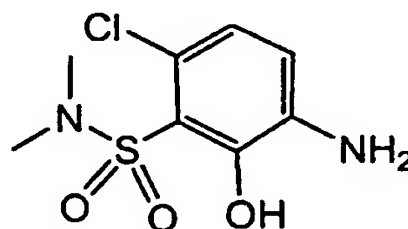
Following the procedures set forth in Example 401, but using commercially available amines, hydroxy-amino-thiophene products in the Table below were obtained.

Prep Ex.	Amine	Product	Yield MH ⁺
402	(Bn) ₂ NH		10% 375.1
403	Me(Bn)NH		14% 299.0
404	Et(Bn)NH		22%
405	(Et) ₂ NH		25%

PREPARATIVE EXAMPLE 406

5

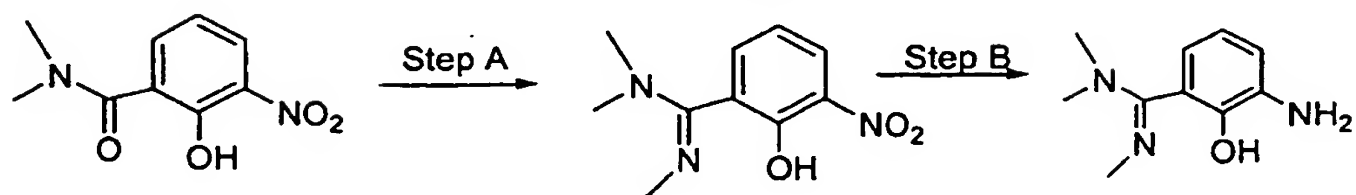
The amine was prepared following the procedure disclosed in WO 01/68570.

PREPARATIVE EXAMPLE 407

The amine was prepared following the procedure disclosed in WO 01/68570.

10

160
PREPARATIVE EXAMPLE 408



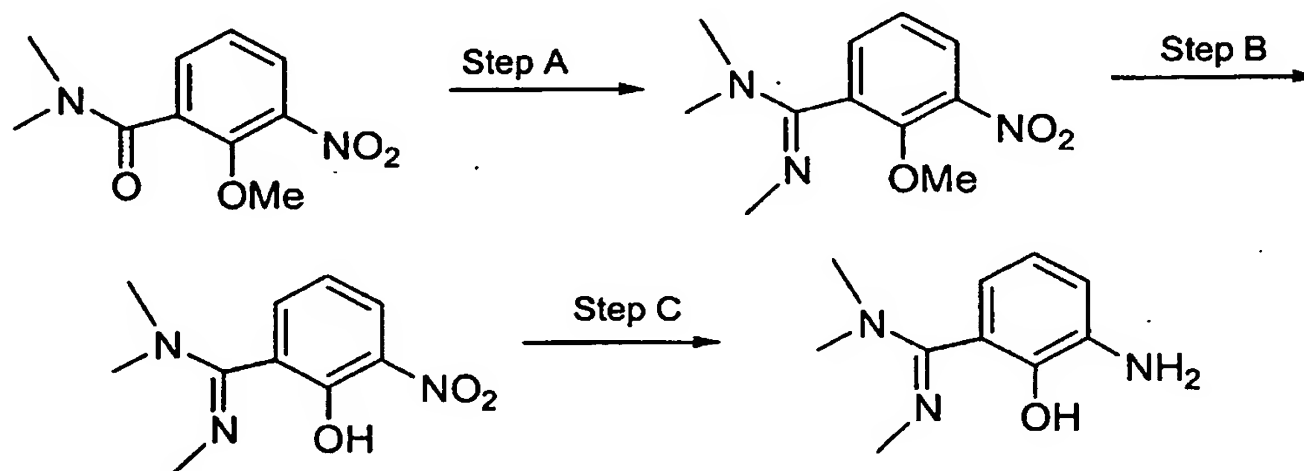
Step A

By using the nitro-amide from Preparative Example 25, Step A, the amidine structure can be prepared following a similar procedure to that in *Tetrahedron Lett.*, 2000, 41 (11), 1677-1680.

Step B

By using the product from Step A and the procedure set forth in Preparative Example 2, Step B, one could obtain the desired amine-amidine.

ALTERNATE PREPARATIVE EXAMPLE 409



Step A

By treating the nitro-amide from Preparative Example 25, Step A with NaH and MeI in refluxing THF, and subsequently, following removal of THF by distillation, with POCl₃ followed by MeNH₂, according to procedures known in the art, one would obtain the desired compound.

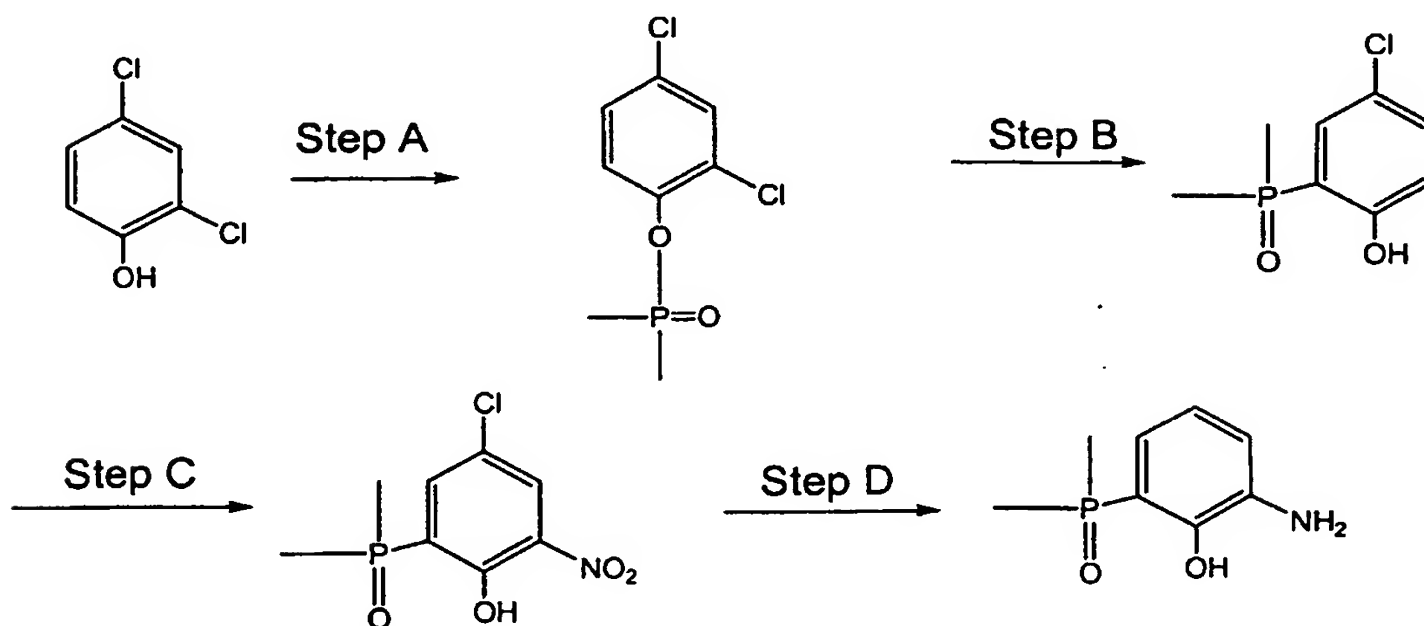
Step B

By treating the product from Step A with BBr₃ in dichloromethane, according to a similar procedure set forth in the literature, one could obtain the desired compound.

Step C

By using the product from Step B and the procedure set forth in Preparative Example 2 Step B, one would obtain the desired compound.

5

PREPARATIVE EXAMPLE 410Step A

10

By following a similar procedure as that described in *Zh. Obshch. Khim.*, 27, 1957, 754, 757., but instead using 2,4-dichlorophenol and dimethylphosphinic chloride, one would obtain the desired compound.

Step B

15

By following a similar procedure as that described in *J. Organomet. Chem.*; 317, 1986, 11-22, one would obtain the desired compound.

Step C

20

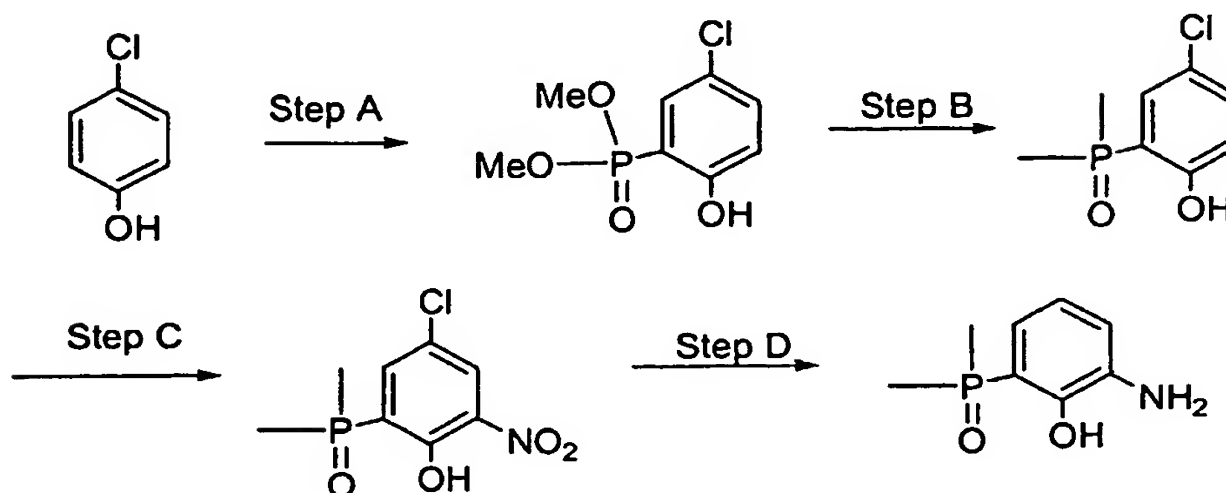
By following a similar procedure as that described in *J. Amer. Chem. Soc.*, 77, 1955, 6221, one would obtain the desired compound.

Step D

By following a similar procedure as that described in *J. Med. Chem.*, 27, 1984, 654-659, one would obtain the desired compound.

25

162
ALTERNATE PREPARATIVE EXAMPLE 411



5 Step A

By following a similar procedure as that described in *Phosphorous, Sulfur Silicon Relat. Elem.*; EN; 61, 12, 1991, 119-129, but instead using 4-chlorophenol, one would obtain the desired compound.

10 Step B

By using a similar procedure as that in *Phosphorous, Sulfur Silicon Relat. Elem.*; EN; 61, 12, 1991, 119-129, but instead using MeMgBr, the desired compound could be prepared.

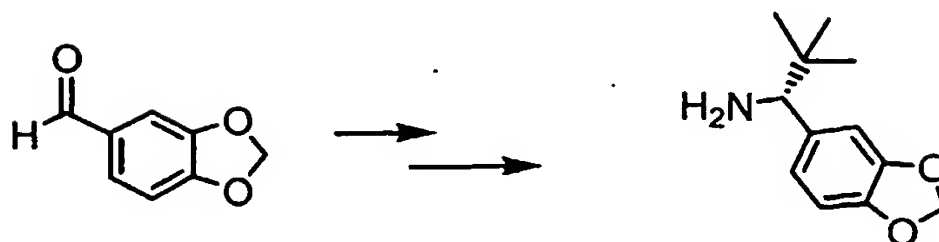
15 Step C

By following a similar procedure as that described in *J. Amer. Chem. Soc.*, 77, 1955, 6221, one would obtain the desired compound.

Step D

20 By following a similar procedure as that described in *J. Med. Chem.*, 27, 1984, 654-659, one would obtain the desired compound.

163
PREPARATIVE EXAMPLES 412

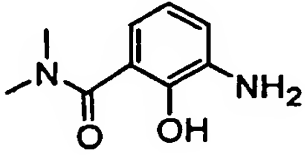
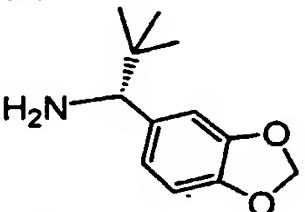
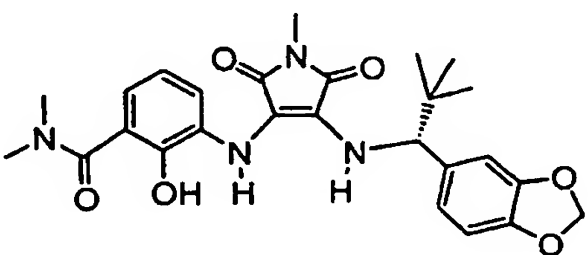
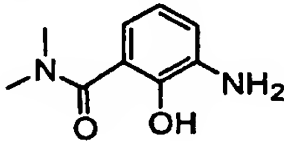
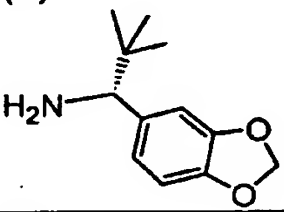
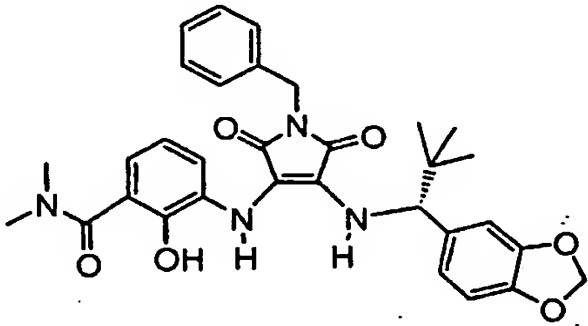
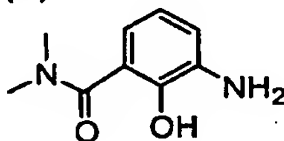
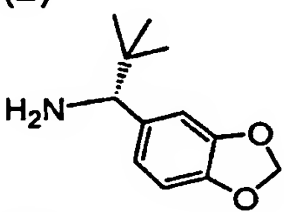
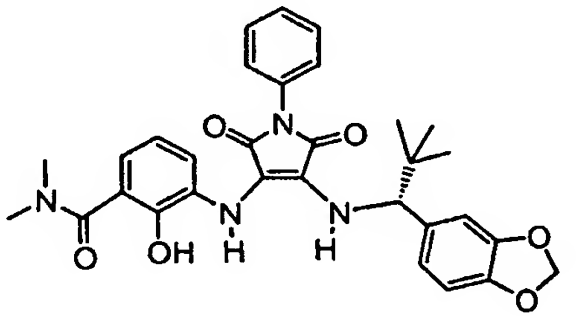
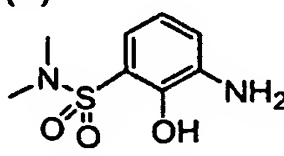
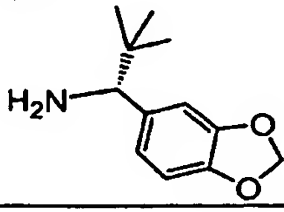
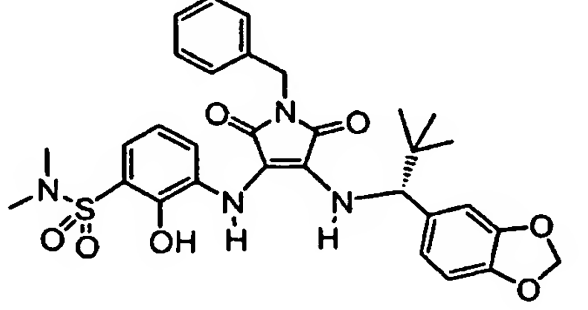


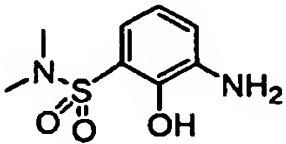
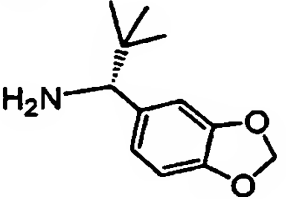
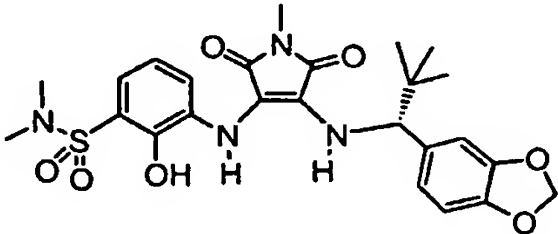
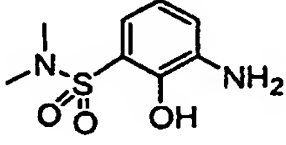
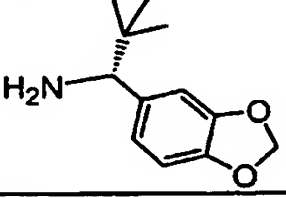
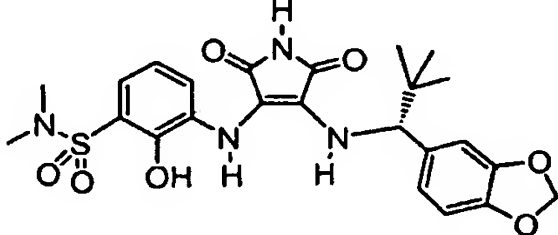
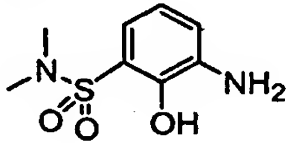
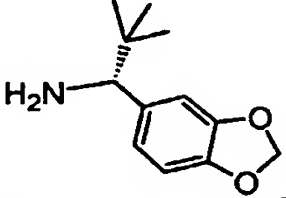
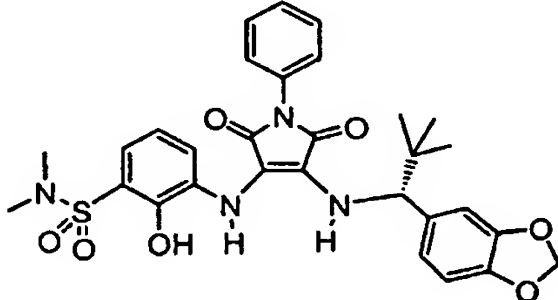
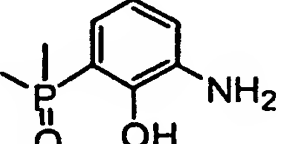
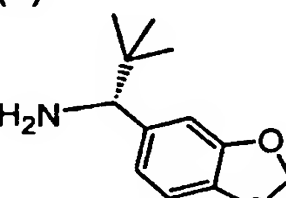
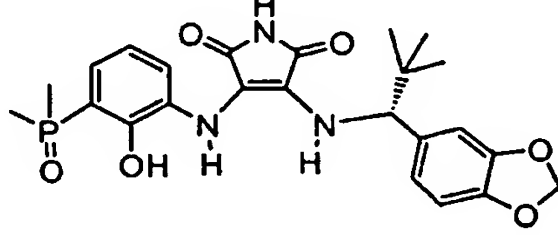
5 Following a similar procedure set forth in Preparative Example 270 but using the commercially available aldehyde shown above in Step A and only tert-butyllithium in Step C, the optically pure amine product was obtained (65%).

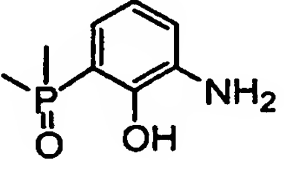
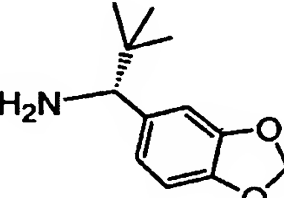
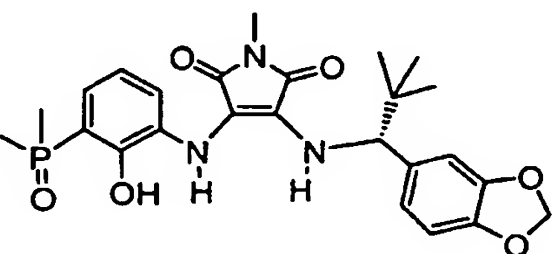
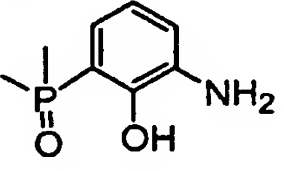
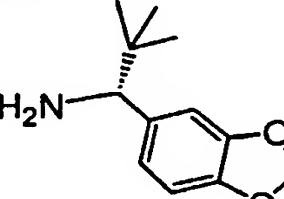
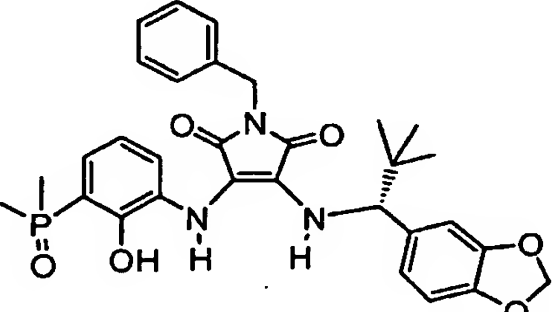
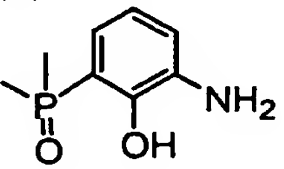
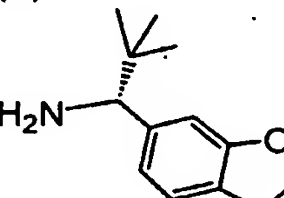
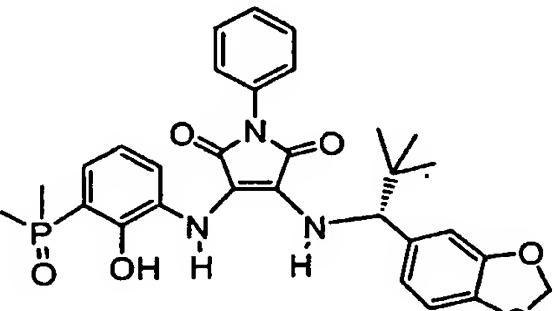
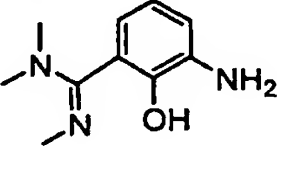
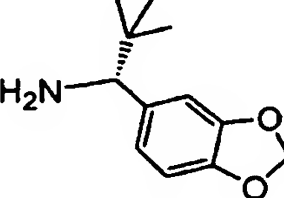
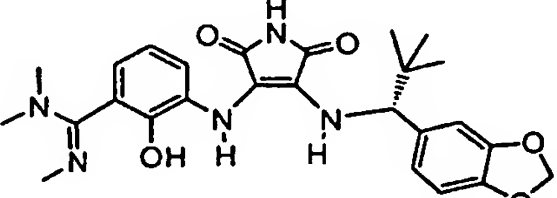
EXAMPLES 702-741

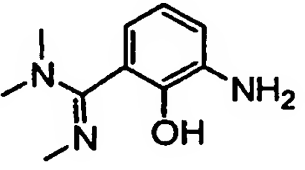
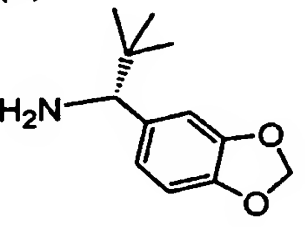
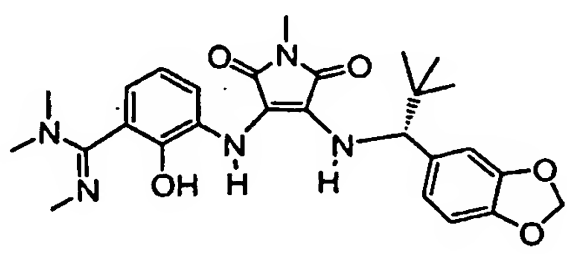
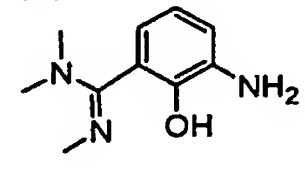
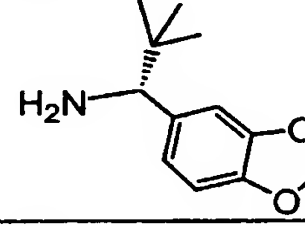
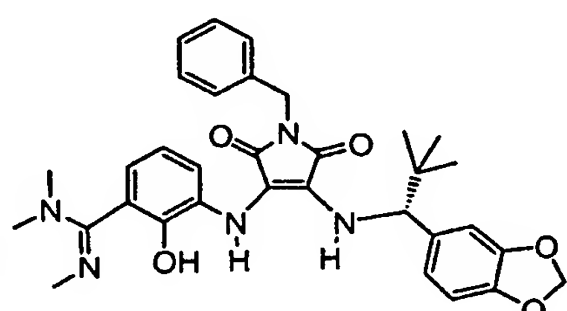
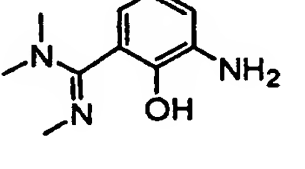
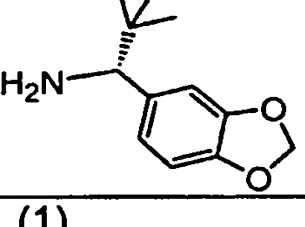
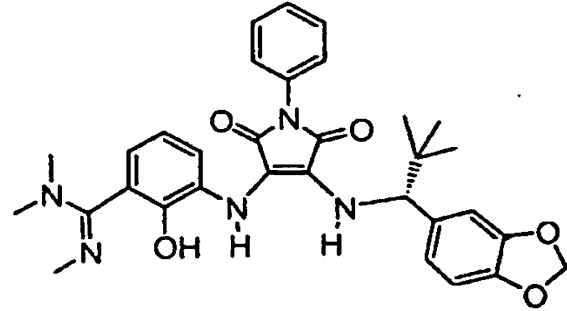
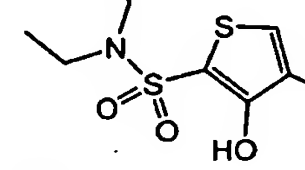
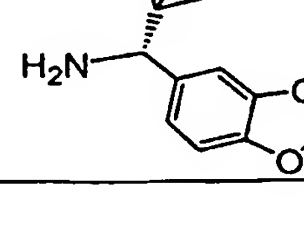
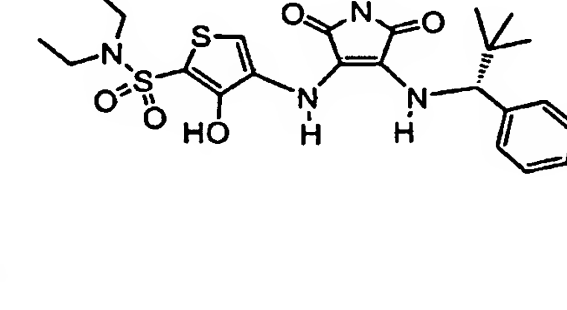
10 If one were to follow the procedure set forth in Preparative Example 50 using the Amine (B-NH₂) and the Dichloride from the Preparative Example indicated, and subsequently treat with the Amine (A-NH₂) according to the procedure used in Example 500, one would obtain the Product indicated in the Table below.

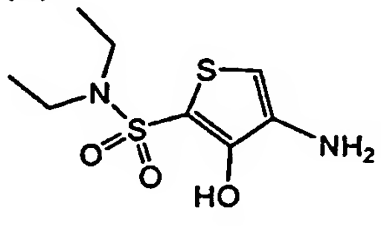
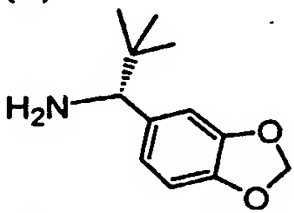
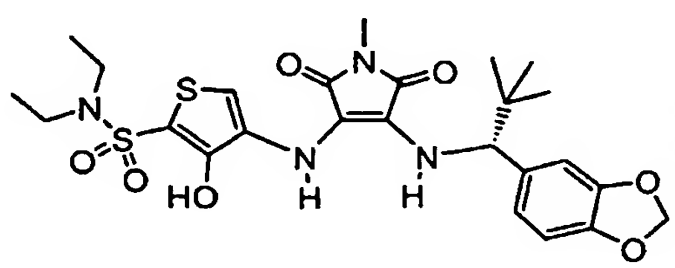
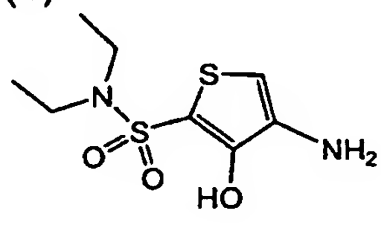
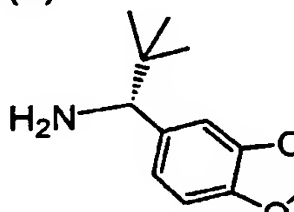
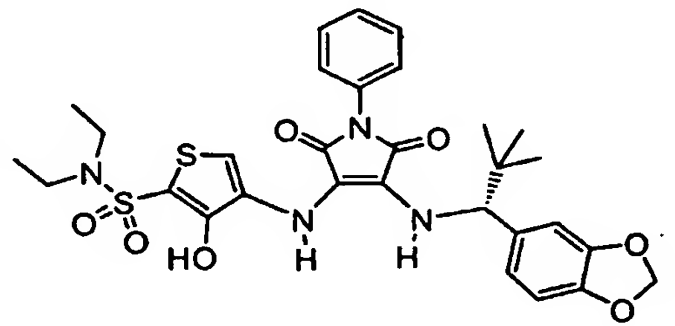
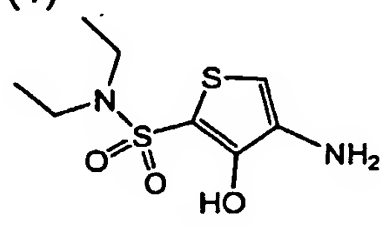
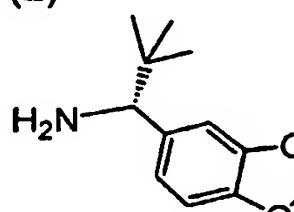
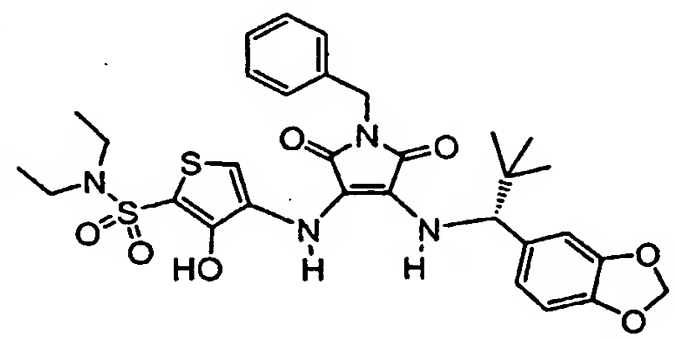
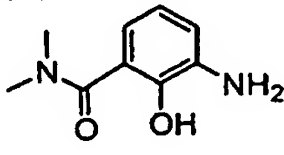
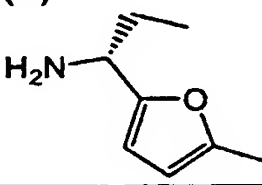
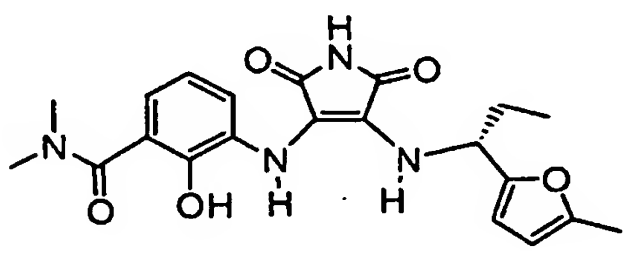
Ex.	Amine (1) (B-NH ₂) (2) (A-NH ₂)	Prep Ex of Dichlori de	Product
702	(1) (2) 	40	

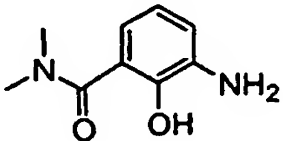
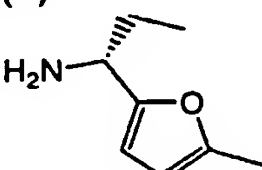
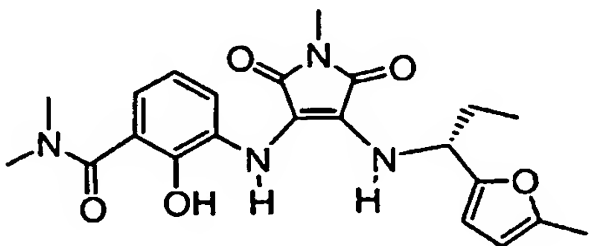
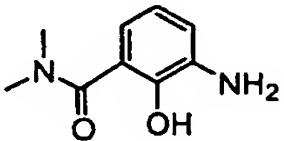
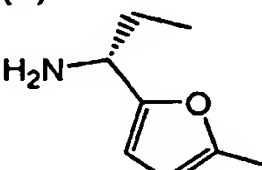
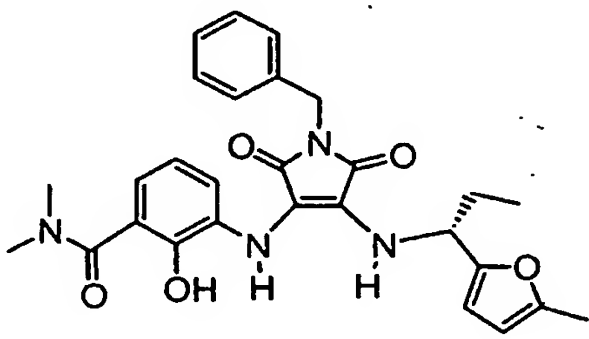
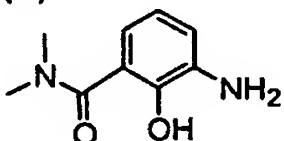
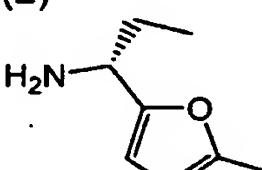
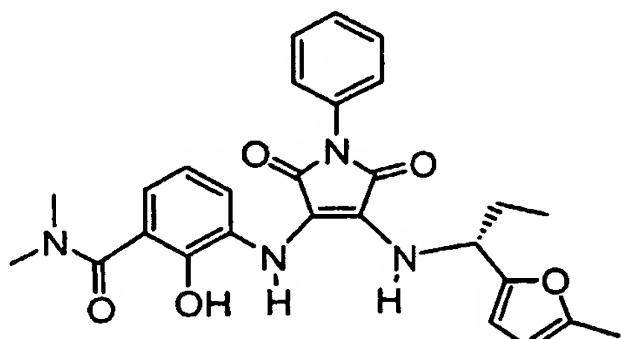
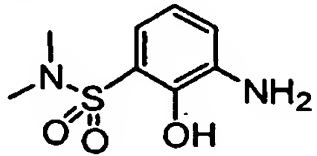
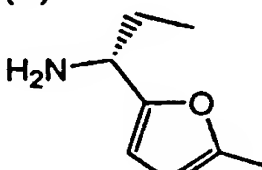
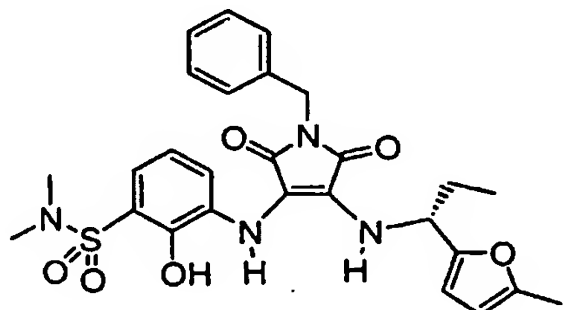
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704	<p>(1)</p>  <p>(2)</p> 	43	
705	<p>(1)</p>  <p>(2)</p> 	42	
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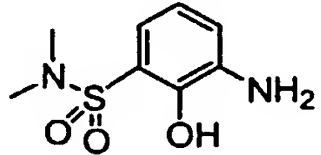
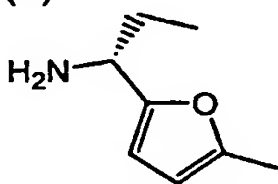
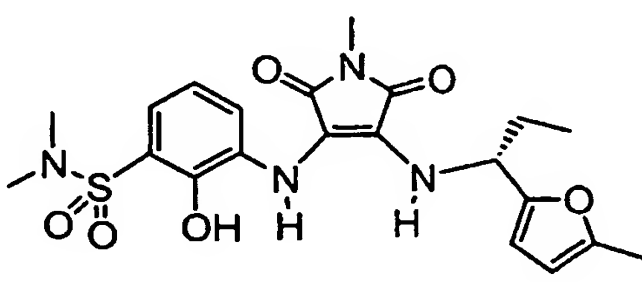
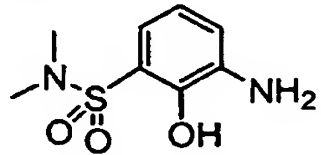
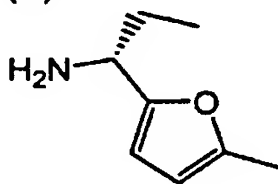
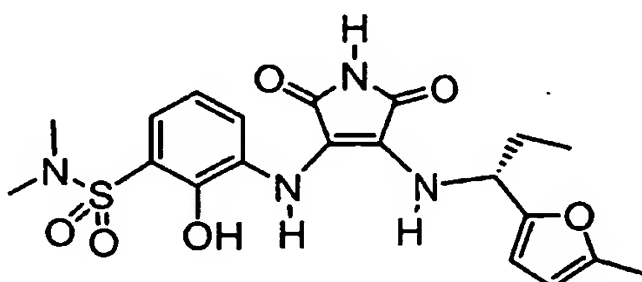
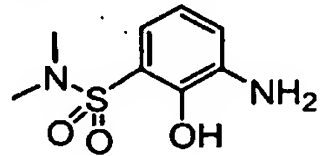
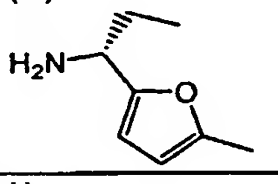
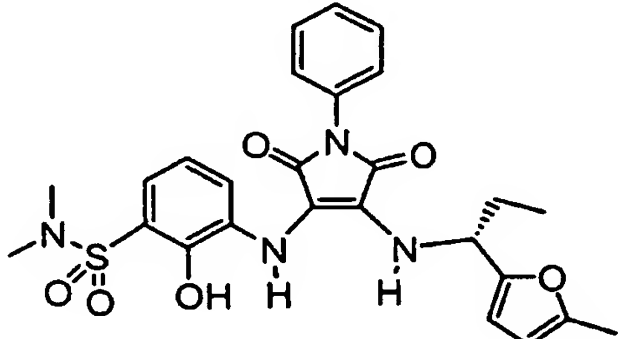
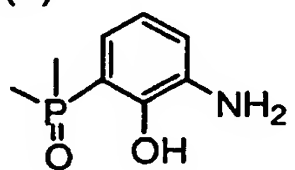
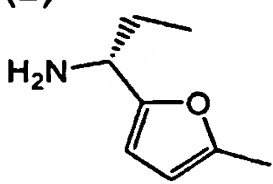
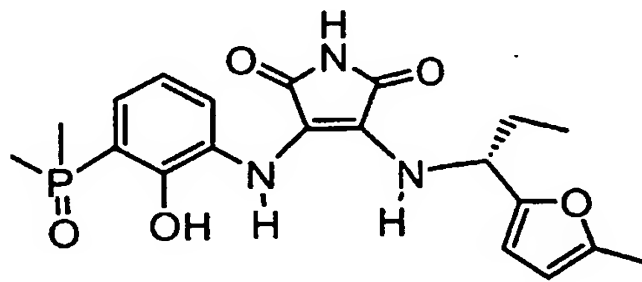
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708	<p>(1)</p>  <p>(2)</p> 	40	
709	<p>(1)</p>  <p>(2)</p> 	42	
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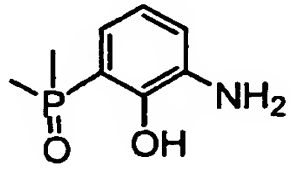
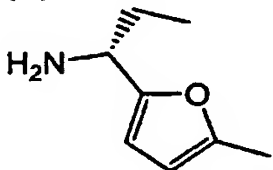
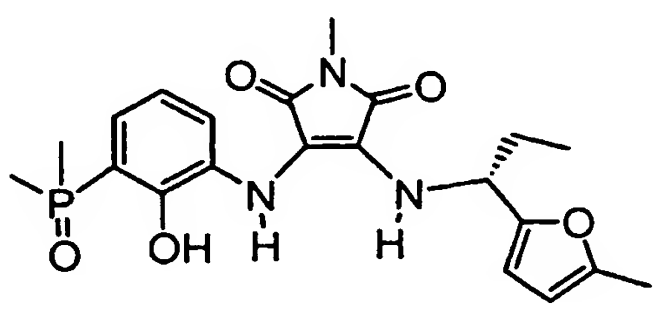
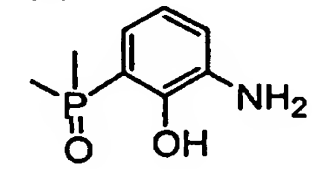
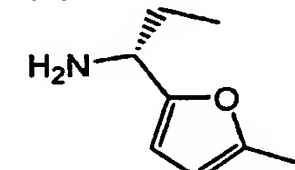
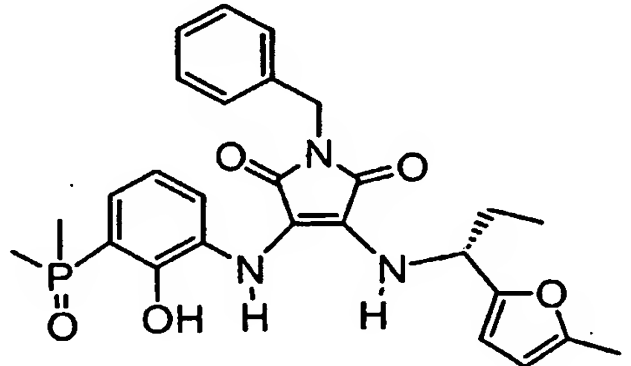
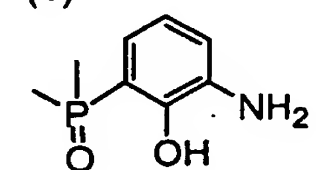
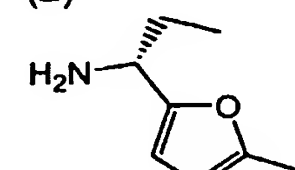
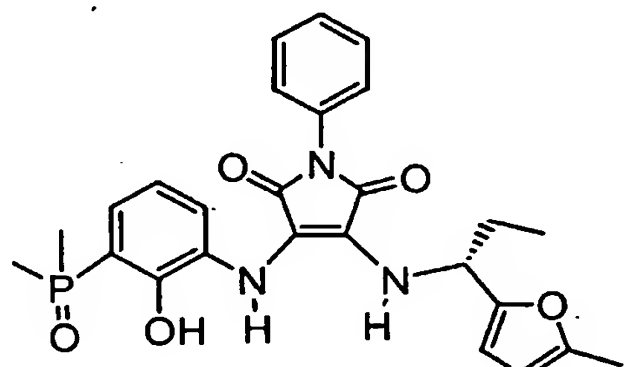
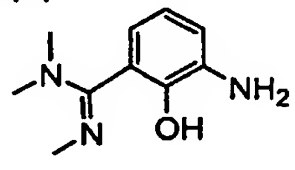
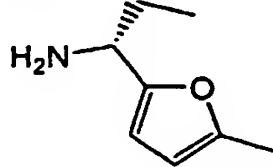
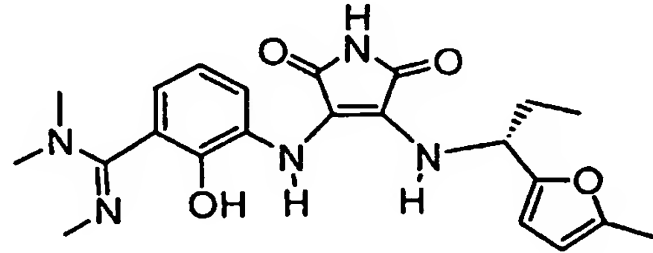
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712	<p>(1)</p>  <p>(2)</p> 	43	
713	<p>(1)</p>  <p>(2)</p> 	42	
714	<p>(1)</p>  <p>(2)</p> 	40	

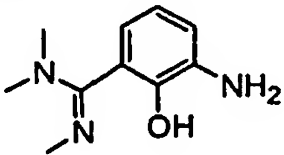
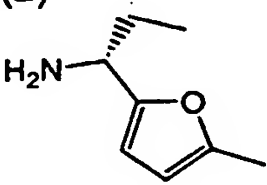
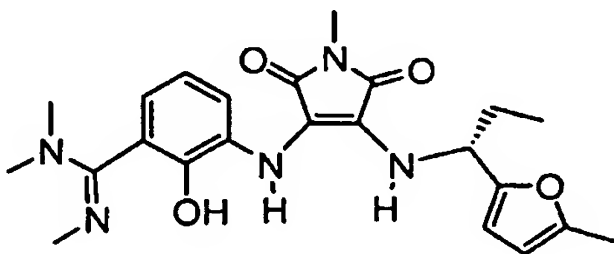
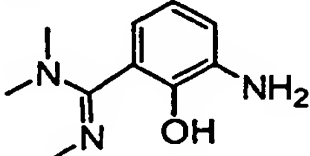
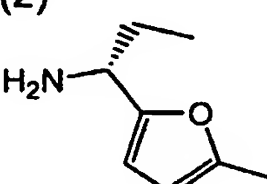
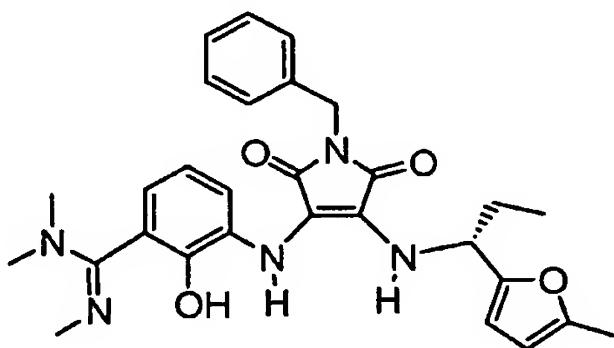
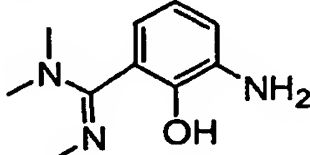
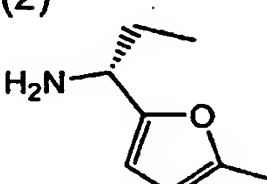
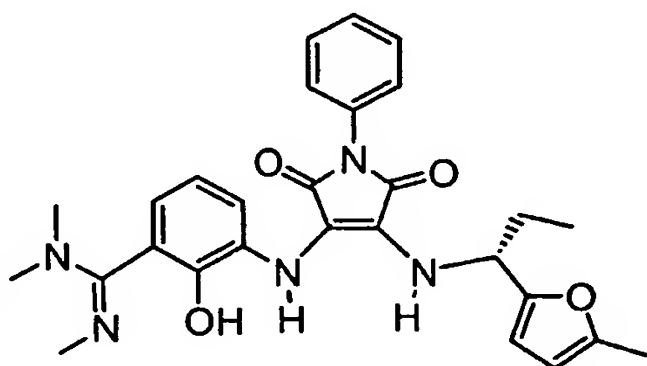
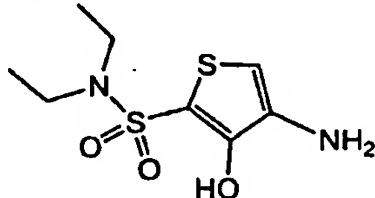
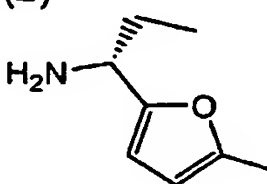
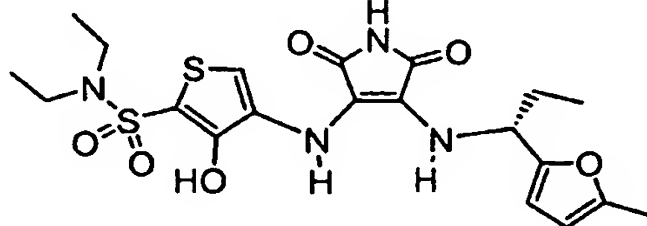
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716	<p>(1)</p>  <p>(2)</p> 	43	
717	<p>(1)</p>  <p>(2)</p> 	42	
718	<p>(1)</p>  <p>(2)</p> 	40	

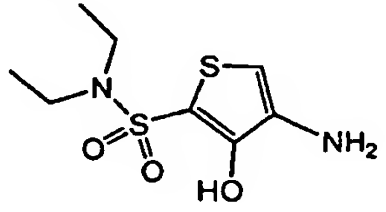
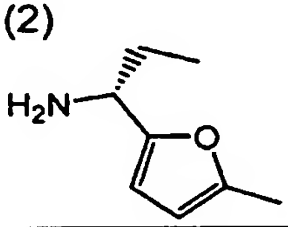
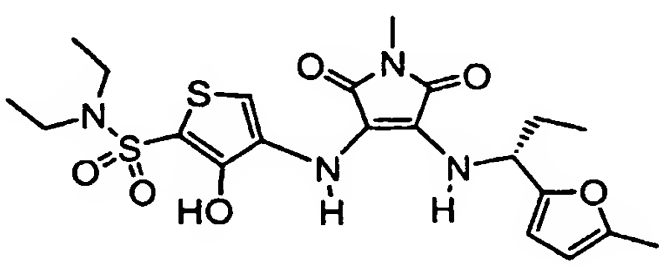
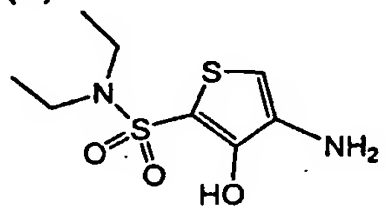
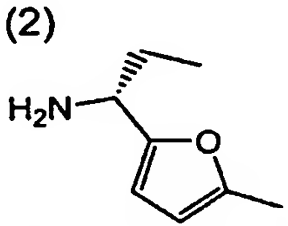
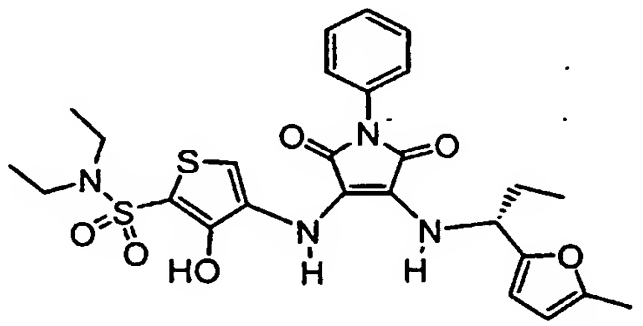
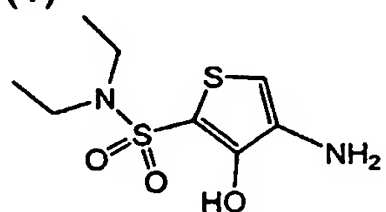
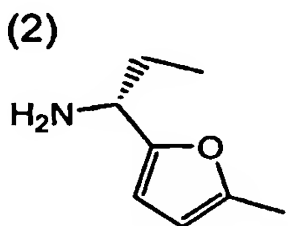
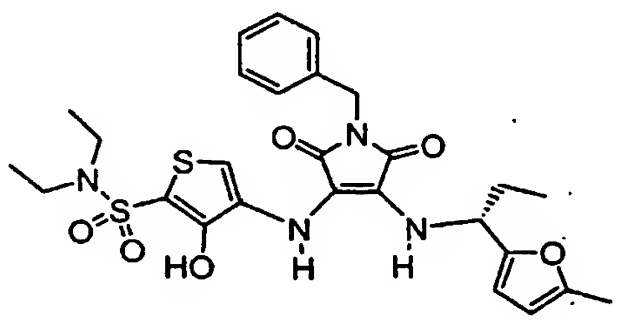
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720	<p>(1)</p>  <p>(2)</p> 	42	
721	<p>(1)</p>  <p>(2)</p> 	43	
722	<p>(1)</p>  <p>(2)</p> 	40	

723	<p>(1)</p>  <p>(2)</p> 	41	
724	<p>(1)</p>  <p>(2)</p> 	43	
725	<p>(1)</p>  <p>(2)</p> 	42	
726	<p>(1)</p>  <p>(2)</p> 	43	

727	<p>(1)</p>  <p>(2)</p> 	41	
728	<p>(1)</p>  <p>(2)</p> 	40	
729	<p>(1)</p>  <p>(2)</p> 	42	
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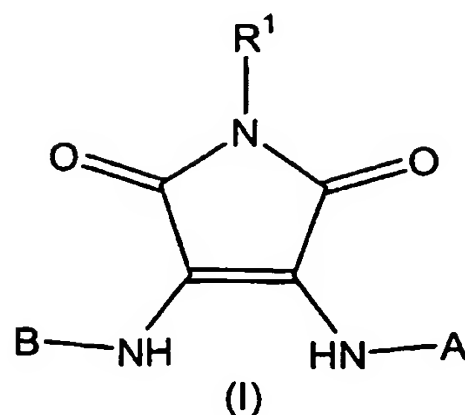
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732	<p>(1)</p>  <p>(2)</p> 	43	
733	<p>(1)</p>  <p>(2)</p> 	42	
734	<p>(1)</p>  <p>(2)</p> 	40	

735	<p>(1)</p>  <p>(2)</p> 	41	
736	<p>(1)</p>  <p>(2)</p> 	43	
737	<p>(1)</p>  <p>(2)</p> 	42	
738	<p>(1)</p>  <p>(2)</p> 	40	

739	<p>(1)</p>  <p>(2)</p> 	41	
740	<p>(1)</p>  <p>(2)</p> 	42	
741	<p>(1)</p>  <p>(2)</p> 	43	

174

Another embodiment of this invention is directed to compounds of the formula (I):



5 or a pharmaceutically acceptable salt or solvate thereof, wherein:

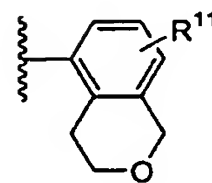
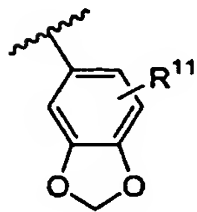
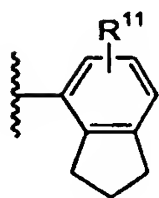
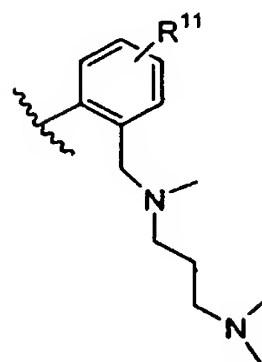
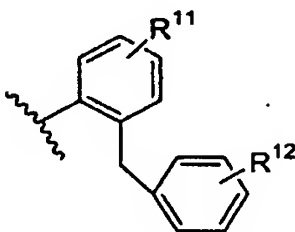
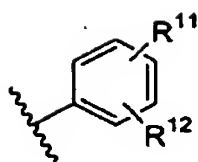
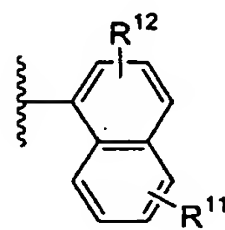
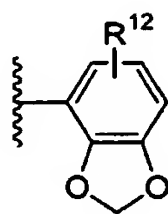
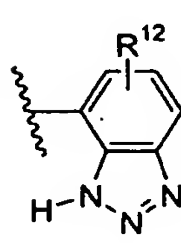
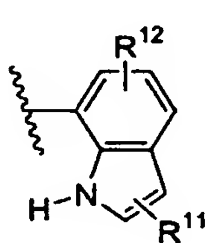
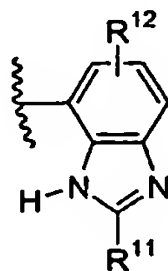
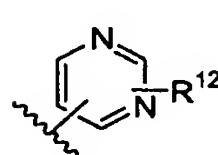
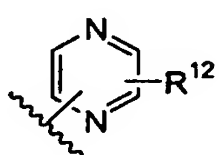
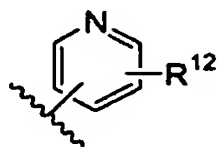
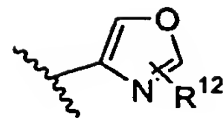
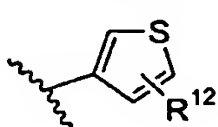
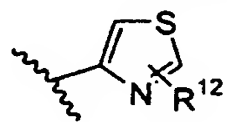
R¹ is selected from the group consisting of: H, aryl, heteroaryl, alkyl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, and heterocycloalkylalkyl; optionally substituted with one or more substituents selected from the group consisting of:

- 10 a) H,
 b) Halogen,
 c) CF₃,
 d) COR¹³,
 e) OH,
 15 f) NR¹³R¹⁴,
 g) NO₂,
 h) Cyano,
 i) -Si(alkyl),
 j) -Si(aryl),
 20 k) SO₂OR¹³,
 l) CO₂R¹³,
 m) CONR¹³R¹⁴,
 n) SO₂NR¹³R¹⁴,
 o) SO₂R¹³,
 25 p) -OR¹³,
 r) -NR¹³R¹⁴,
 s) -O(C=O)R¹³,
 t) -O(C=O)NR¹³R¹⁴,
 u) -NR¹³COR¹⁴ and

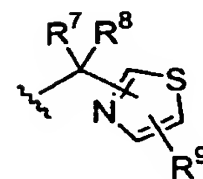
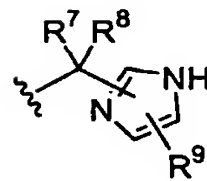
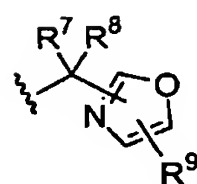
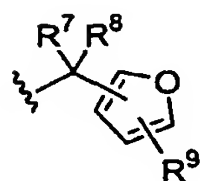
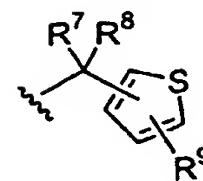
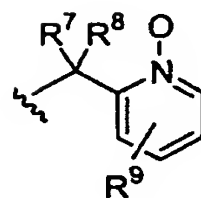
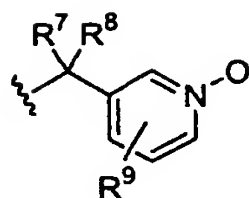
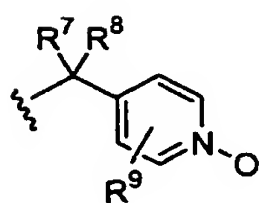
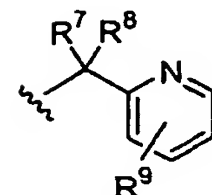
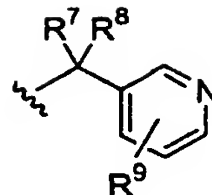
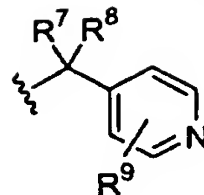
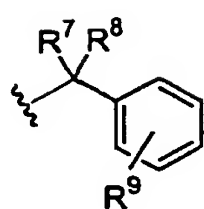
175

v) $-NR^{13}CO_2R^{14}$;

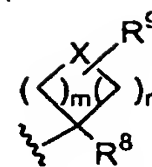
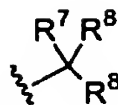
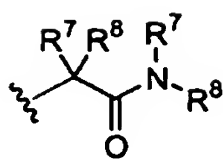
A is selected from the group consisting of:



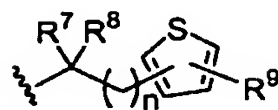
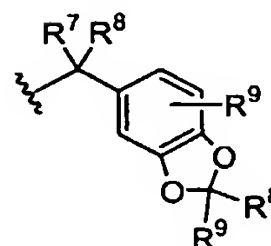
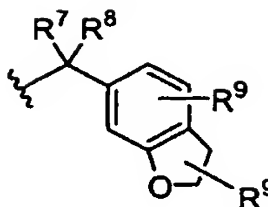
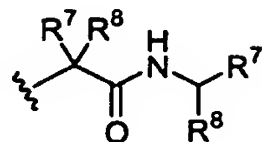
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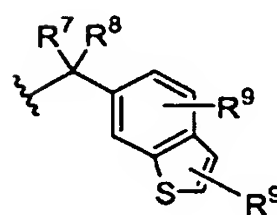
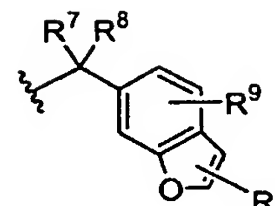
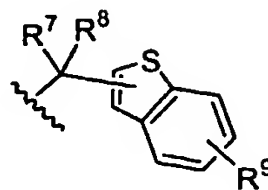
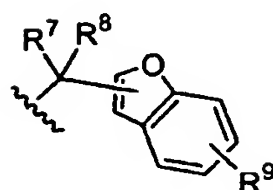
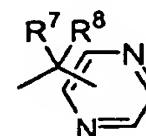
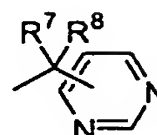
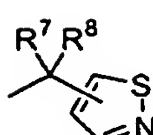
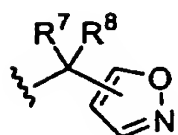
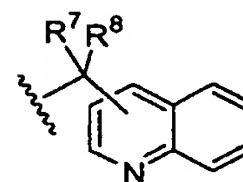
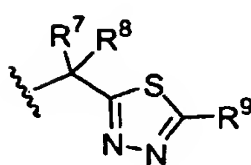
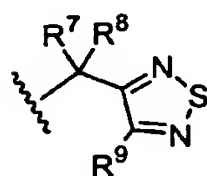
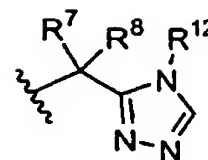
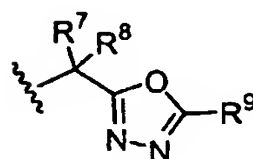
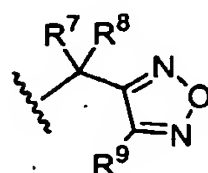
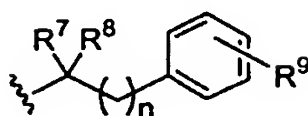
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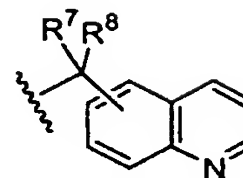
m = 1 - 5
n = 0 - 4
X = C, O, N, S



n = 0 - 6

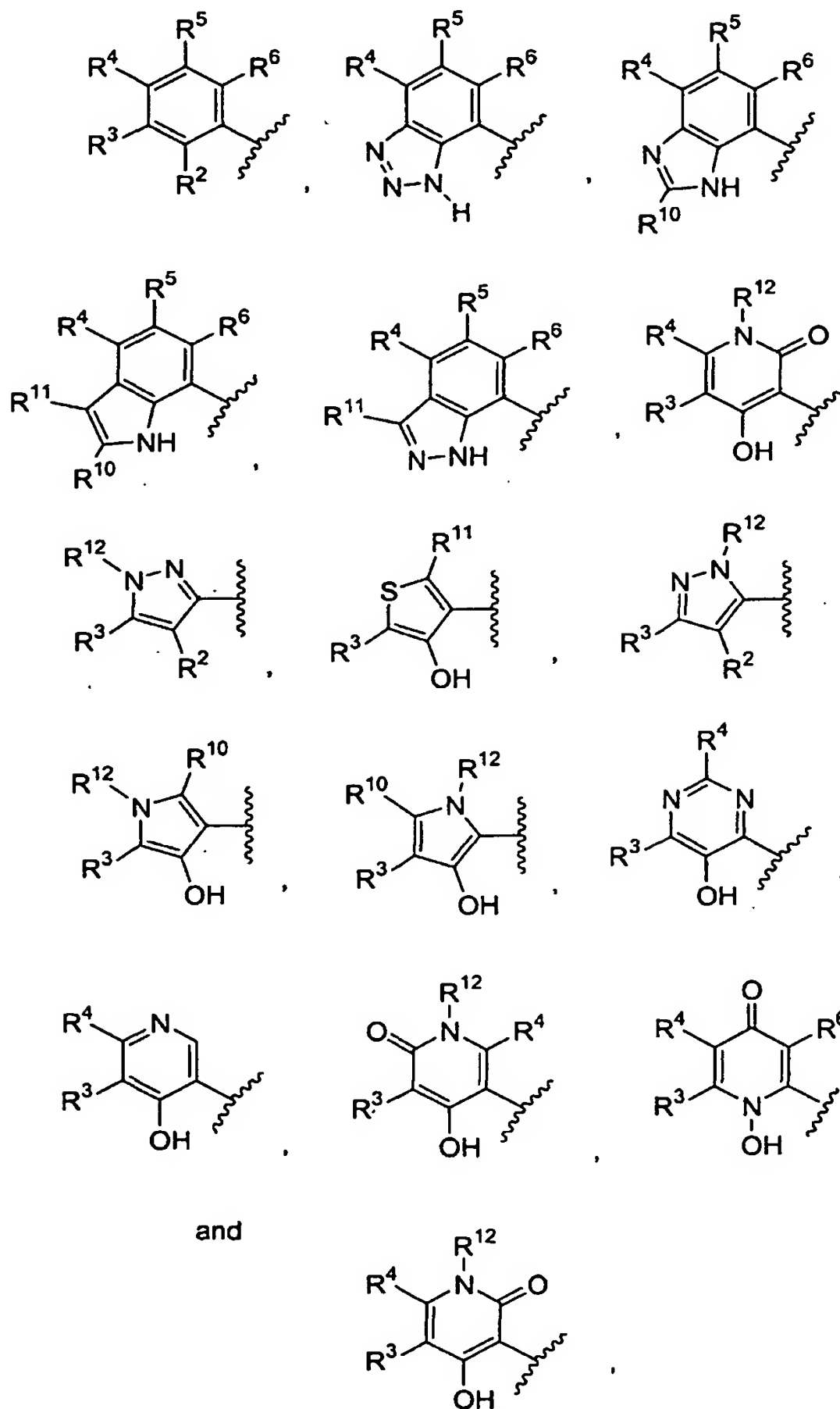


and



and

B is an optionally substituted aryl or heteroaryl group selected from the group consisting of:



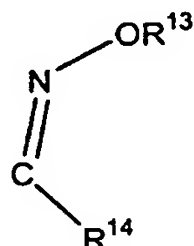
and

5 wherein,

R^2 is selected from the group consisting of hydrogen, OH, C(O)OH, SH, $\text{SO}_2\text{NR}^{13}\text{R}^{14}$, NHC(O)R^{13} , $\text{NHSO}_2\text{NR}^{13}\text{R}^{14}$, $\text{NHSO}_2\text{R}^{13}$, $\text{NR}^{13}\text{R}^{14}$, C(O)NR¹³R¹⁴,

¹⁷⁹
 $C(O)NHOR^{13}$, $C(O)NR^{13}OH$, $OC(O)R^{13}$ and an optionally substituted cyclic or heterocyclic acidic functional group, with the proviso that if R^2 is $SO_2NR^{13}R^{14}$, at least one of R^{13} and R^{14} must be hydrogen;

R^3 and R^4 are independently selected from the group consisting of hydrogen,
 5 halogen, alkyl, alkoxy, OH, CF_3 , OCF_3 , NO_2 , $C(O)R^{13}$, $C(O)OR^{13}$, $C(O)NR^{13}R^{14}$,



$SO_{(t)}NR^{13}R^{14}$, $SO_{(t)}R^{13}$, $C(O)NR^{13}OR^{14}$, , cyano, and optionally substituted aryl or heteroaryl, wherein the substituents on said optionally substituted groups are independently selected from the group consisting of R^9 substituents.

R^5 and R^6 are independently selected from the group consisting of hydrogen,
 10 halogen, alkyl, alkoxy, CF_3 , OCF_3 , NO_2 , $C(O)R^{13}$, $C(O)OR^{13}$, $C(O)NR^{13}R^{14}$, $SO_{(t)}NR^{13}R^{14}$, $C(O)NR^{13}OR^{14}$, cyano, and an optionally substituted aryl or heteroaryl group, wherein the substituents on said optionally substituted groups are independently selected from the group consisting of R^9 substituents;

R^7 and R^8 are the same or different and are independently selected from the
 15 group consisting of H; optionally substituted or unsubstituted alkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, CO_2R^{13} , $CONR^{13}R^{14}$, fluoroalkyl, alkynyl, alkenyl, alkynylalkyl, alkenylalkyl, and cycloalkenyl, wherein said substituents on said substituted groups are selected from the group consisting of:

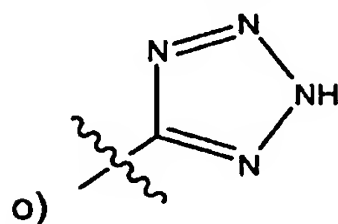
- 20 a) H,
 b) Halogen,
 c) CF_3 ,
 d) COR^{13} ,
 e) OH,
 25 f) $NR^{13}R^{14}$,
 g) NO_2 ,
 h) Cyano,
 i) $-Si(\text{alkyl})$,
 j) $-Si(\text{aryl})$,
 30 k) SO_2OR^{13} ,

180

- l) CO_2R^{13} ,
 m) $\text{CONR}^{13}\text{R}^{14}$,
 n) $\text{SO}_2\text{NR}^{13}\text{R}^{14}$,
 o) SO_2R^{13} ,
 5 p) $-\text{OR}^{13}$,
 r) $-\text{NR}^{13}\text{R}^{14}$,
 s) $-\text{O}(\text{C}=\text{O})\text{R}^{13}$,
 t) $-\text{O}(\text{C}=\text{O})\text{NR}^{13}\text{R}^{14}$,
 u) $-\text{NR}^{13}\text{COR}^{14}$ and
 10 v) $-\text{NR}^{13}\text{CO}_2\text{R}^{14}$;

Each R^9 is independently selected from the group consisting of:

- a) R^{13} ;
 b) halogen;
 c) $-\text{CF}_3$;
 15 d) $-\text{COR}^{13}$;
 e) $-\text{OR}^{13}$;
 f) $-\text{NR}^{13}\text{R}^{14}$;
 g) $-\text{NO}_2$;
 h) $-\text{CN}$;
 20 i) $-\text{SO}_2\text{R}^{13}$;
 j) $-\text{SO}_2\text{NR}^{13}\text{R}^{14}$;
 k) $-\text{NR}^{13}\text{COR}^{14}$;
 l) $-\text{CONR}^{13}\text{R}^{14}$;
 m) $-\text{NR}^{13}\text{CO}_2\text{R}^{14}$;
 25 n) CO_2R^{13} , and



R^{10} and R^{11} are independently selected from the group consisting of hydrogen, halogen, CF_3 , OCF_3 , $\text{NR}^{13}\text{R}^{14}$, $\text{NR}^{13}\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, OH , $\text{C}(\text{O})\text{OR}^{13}$, SH , $\text{SO}_2\text{NR}^{13}\text{R}^{14}$, SO_2R^{13} , $\text{NHC}(\text{O})\text{R}^{13}$, $\text{NHSO}_2\text{NR}^{13}\text{R}^{14}$, $\text{NHSO}_2\text{R}^{13}$, $\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, $\text{C}(\text{O})\text{NR}^{13}\text{OR}^{14}$, $\text{OC}(\text{O})\text{R}^{13}$ and cyano.

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181

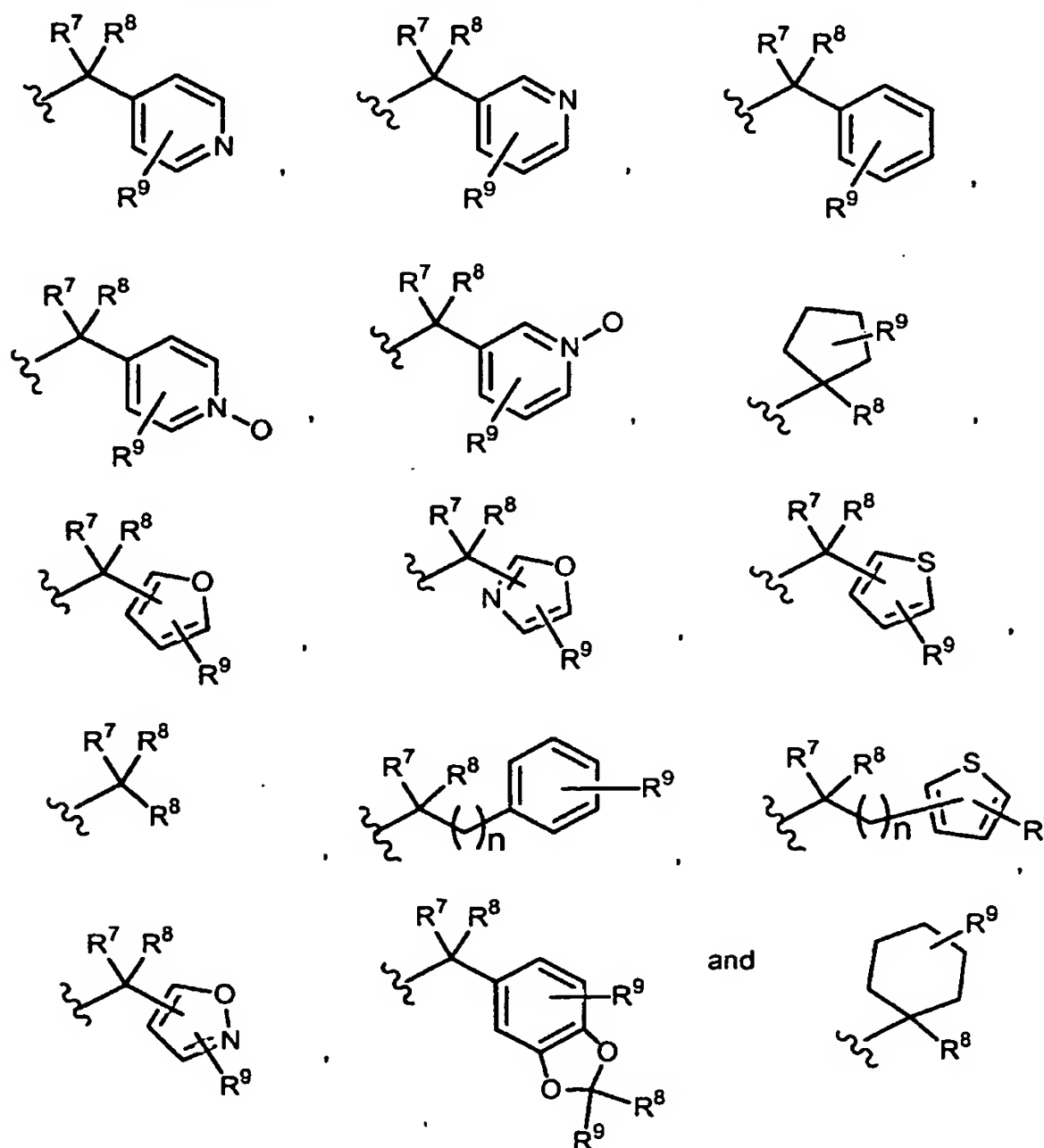
R^{12} is hydrogen, $OC(O)R^{13}$, or an optionally substituted aryl, heteroaryl, arylalkyl, cycloalkyl, alkyl, cycloalkylalkyl or heteroarylalkyl group;

R^{13} and R^{14} are the same or different and are independently selected from the group consisting of H; optionally substituted or unsubstituted alkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, and fluoroalkyl, or R^{13} and R^{14} when taken together form an optionally substituted 3 to 7 membered heterocyclic ring containing one to two heteroatoms selected from O, S and N, and wherein the substituents on the optionally substituted groups are selected from the group consisting of H, alkyl, aryl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, carbonyl and halogen and

t is 1 or 2.

Another embodiment of this invention is directed to compounds described in the preceding embodiment wherein:

A is selected from the group consisting of:



wherein:

R^7 is selected from the group consisting of H, CF_3 , fluoroalkyl, alkyl, cycloalkyl;

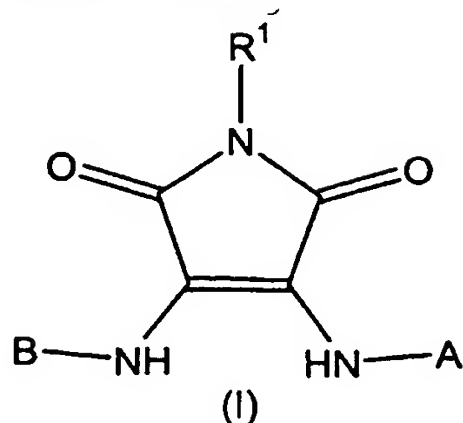
R^8 is selected from the group consisting of H, alkyl, or fluoroalkyl and

5 R^9 is selected from the group consisting of: H, F, Cl, Br, CF_3 , alkyl, or fluoroalkyl.

10 While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

WHAT IS CLAIMED IS:

1. A compound of the formula (I):



- 5 or a pharmaceutically acceptable salt or solvate thereof, wherein:

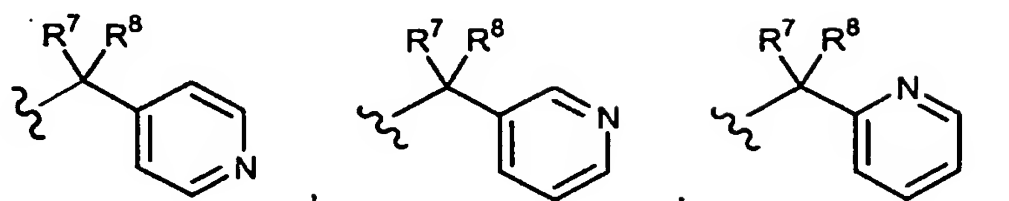
R^1 is selected from the group consisting of: H, aryl, heteroaryl, alkyl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, and heterocycloalkylalkyl; optionally substituted with one or more substituents selected from the group consisting of:

- 10 a) H,
b) Halogen,
c) CF_3 ,
d) COR^{13} ,
e) OH,
15 f) $NR^{13}R^{14}$,
g) NO_2 ,
h) Cyano,
i) $-Si(alkyl)$,
j) $-Si(aryl)$,
20 k) SO_2OR^{13} ,
l) CO_2R^{13} ,
m) $CONR^{13}R^{14}$,
n) $SO_2NR^{13}R^{14}$,
o) SO_2R^{13} ,
25 p) $-OR^{13}$,
r) $-NR^{13}R^{14}$,
s) $-O(C=O)R^{13}$,
t) $-O(C=O)NR^{13}R^{14}$,
u) $-NR^{13}COR^{14}$ and

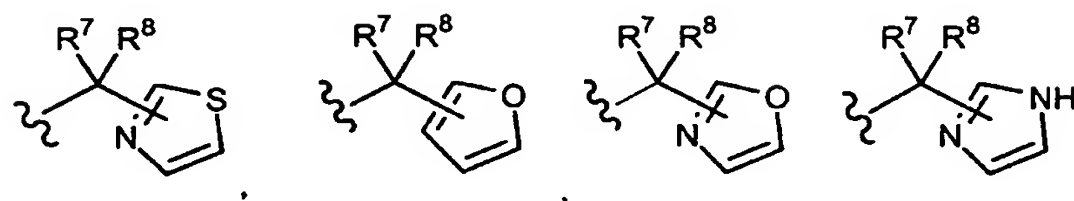
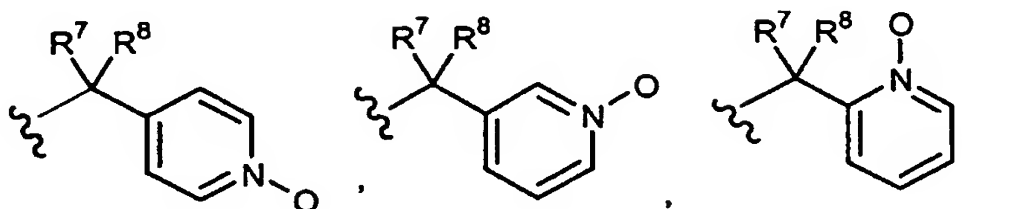
v) $-NR^{13}CO_2R^{14}$;

A is selected from the group consisting of:

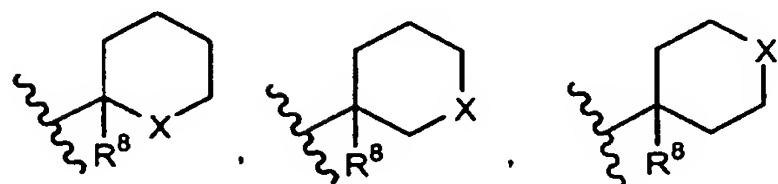
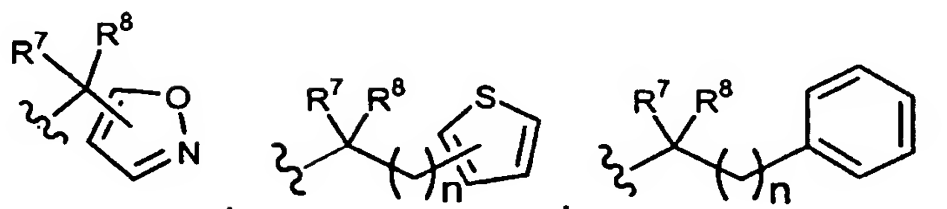
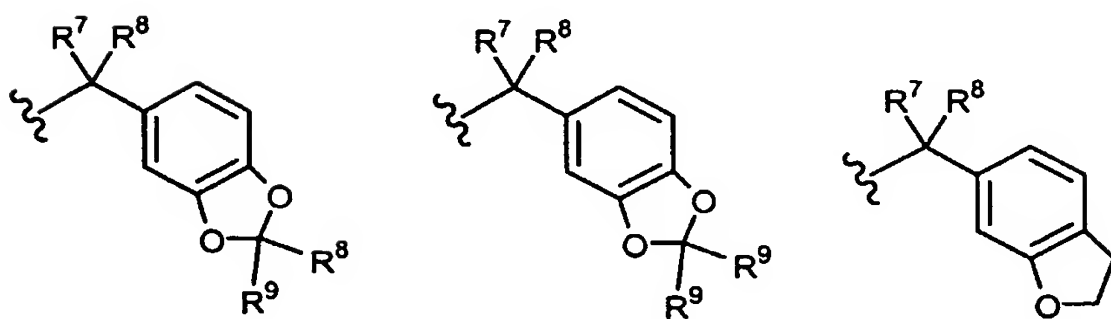
(1)



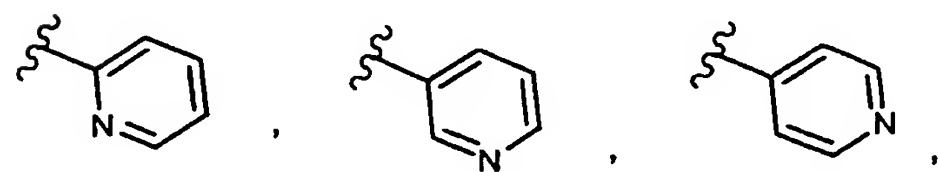
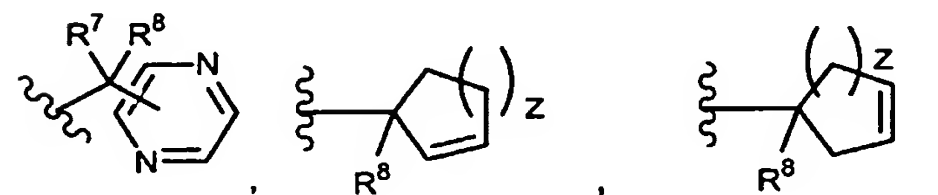
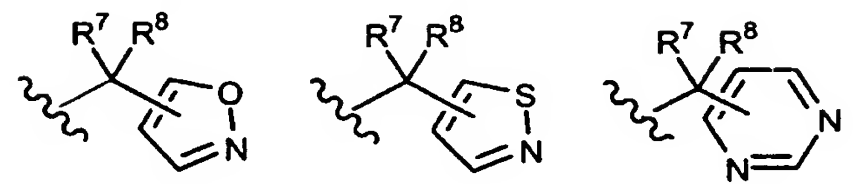
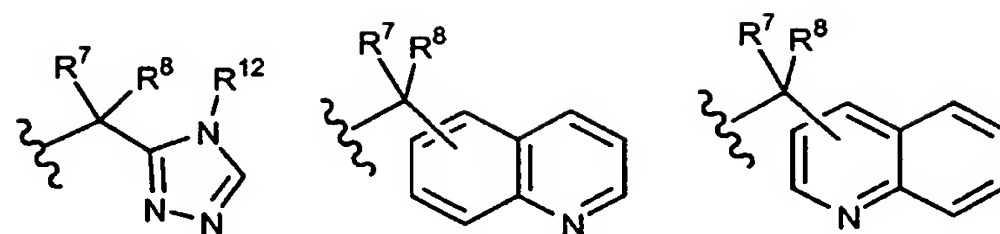
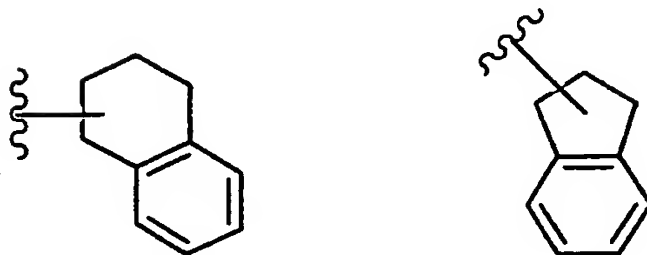
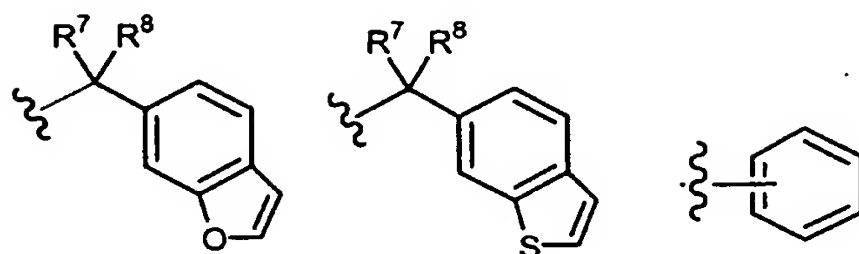
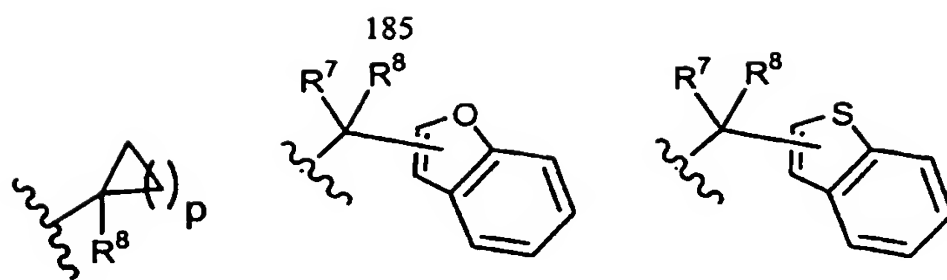
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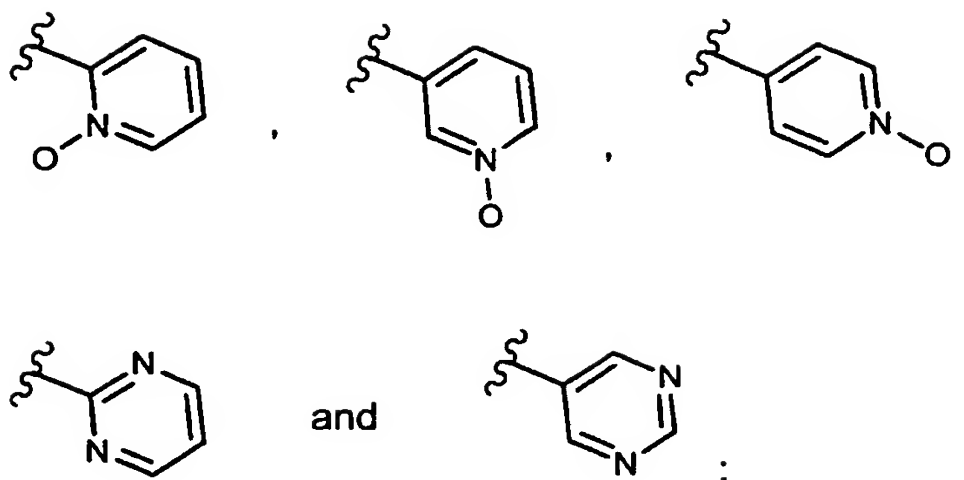
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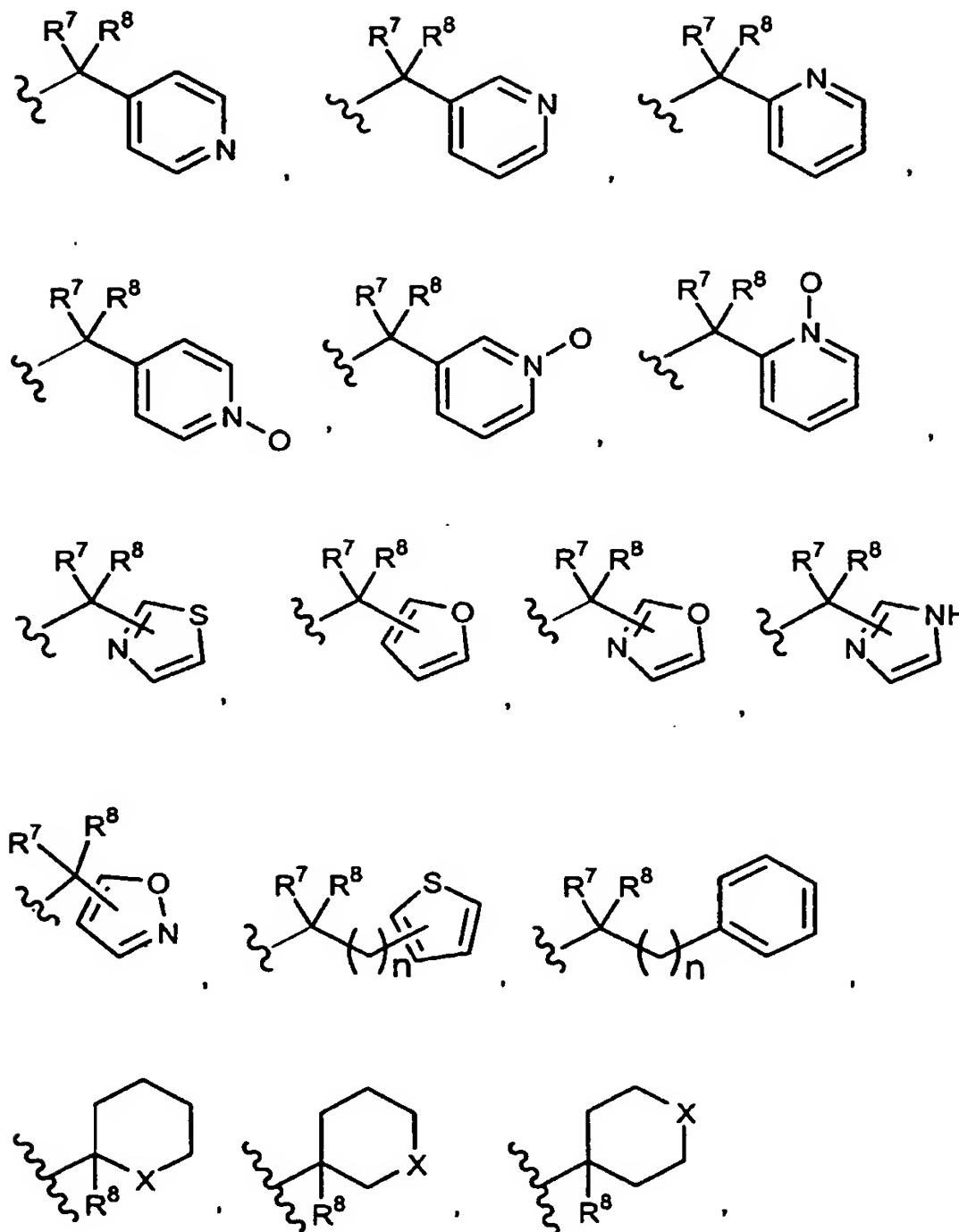
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186



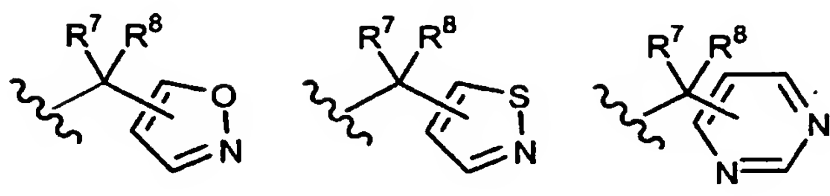
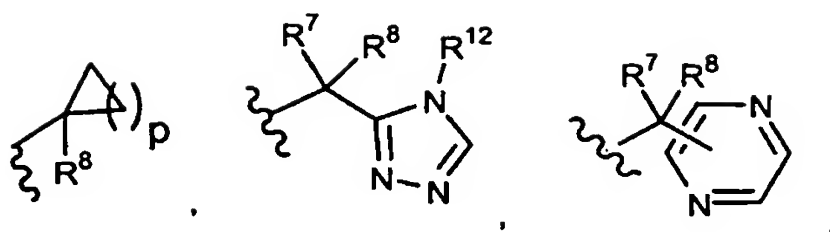
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(2)

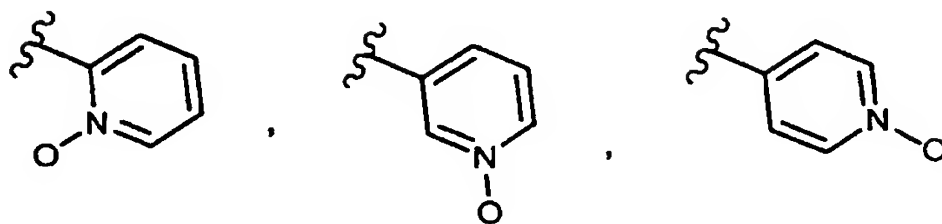
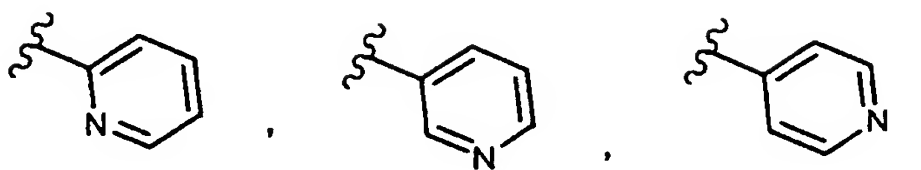
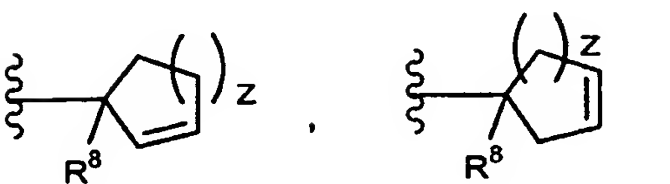


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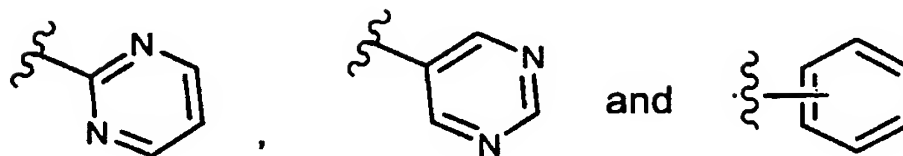
187



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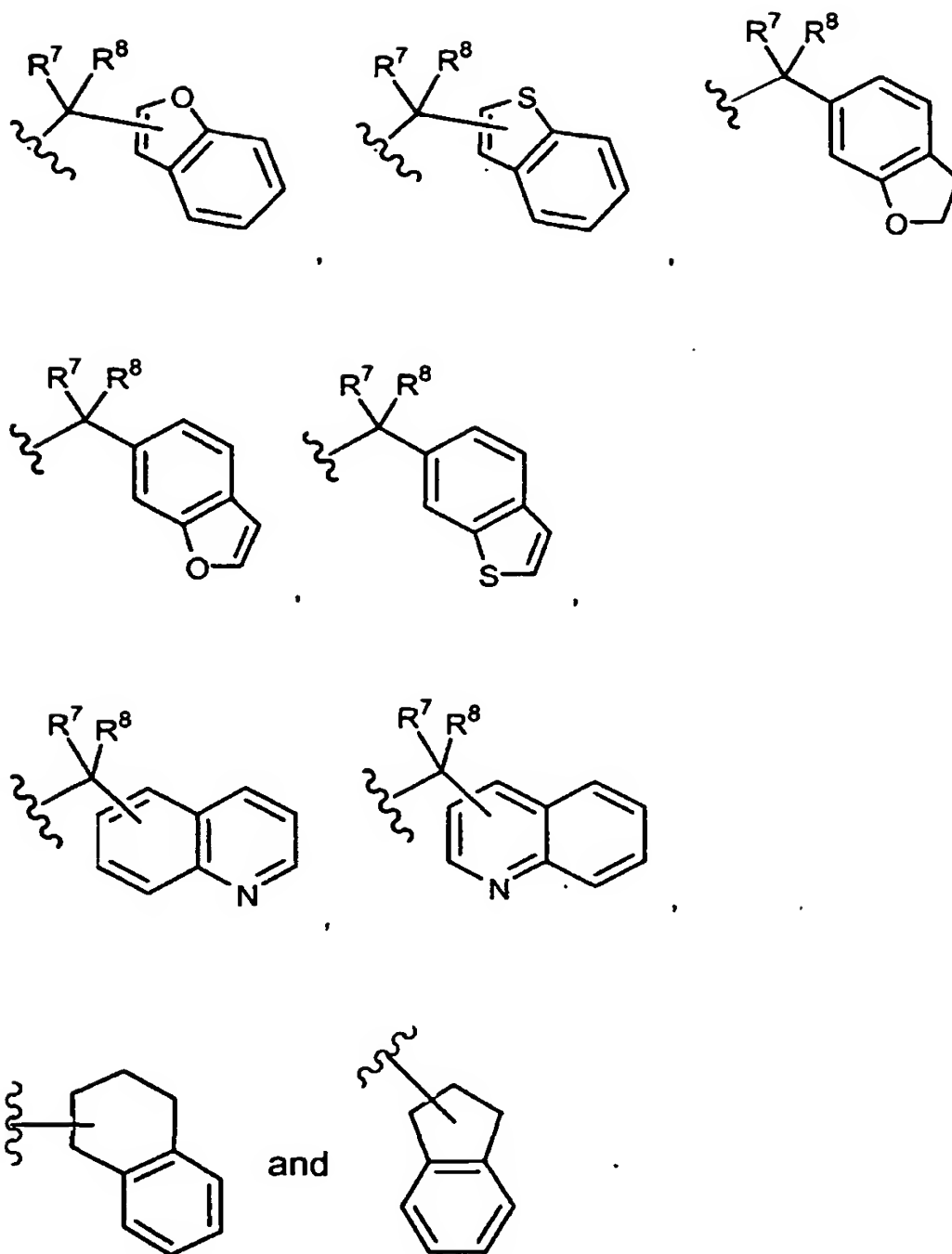


wherein the above rings of said A groups are substituted with 1 to 6 substituents
each independently selected from the group consisting of: R^9 groups;

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188

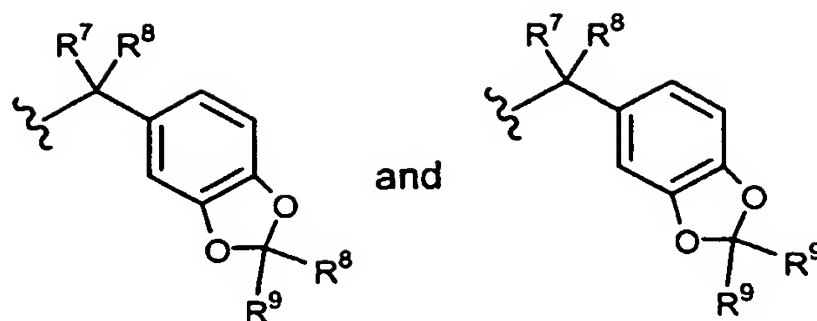
(3)



wherein one or both of the above rings of said A groups are substituted with 1 to 6 substituents each independently selected from the group consisting of: R^9 groups;

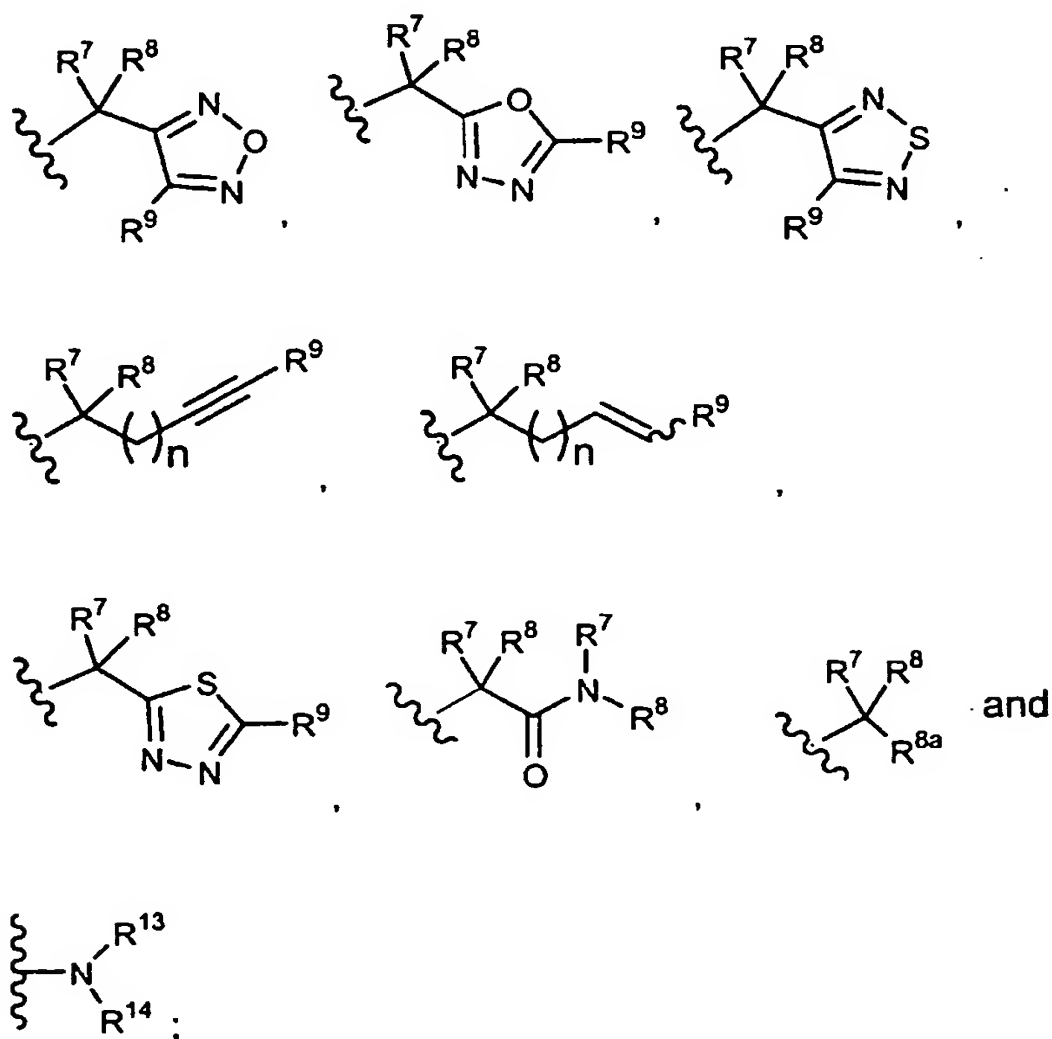
189

(4)



wherein the above phenyl rings of said A groups are substituted with 1 to 3
 substituents each independently selected from the group consisting of: R⁹ groups;
 5 and

(5)

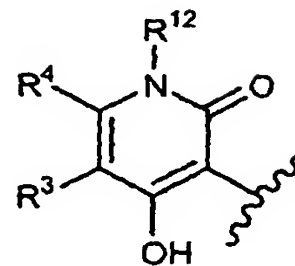
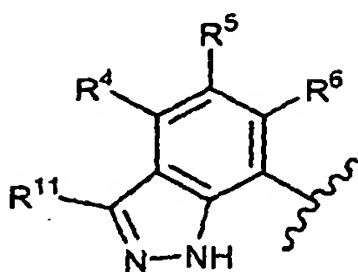
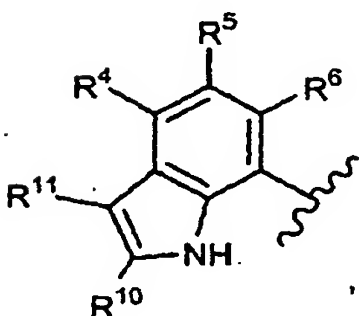
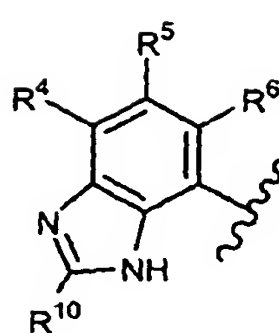
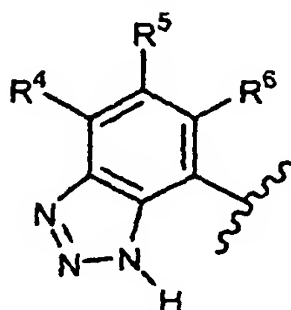
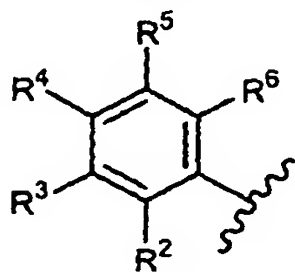


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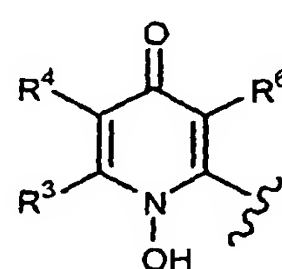
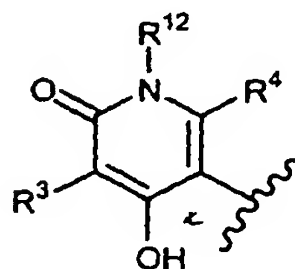
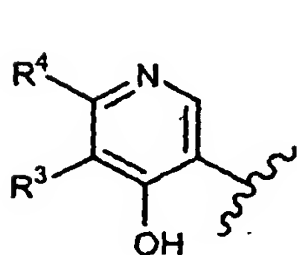
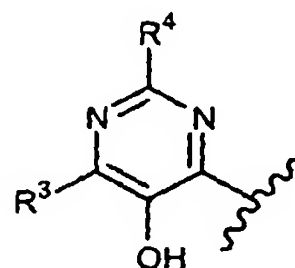
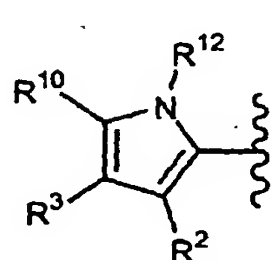
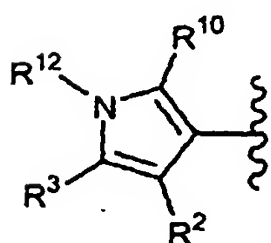
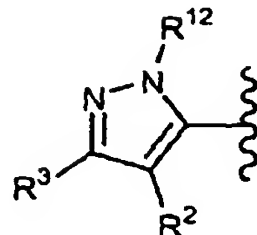
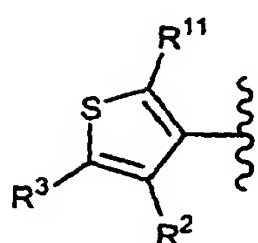
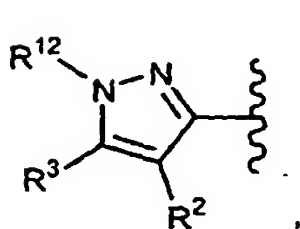
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190

B is selected from the group consisting of

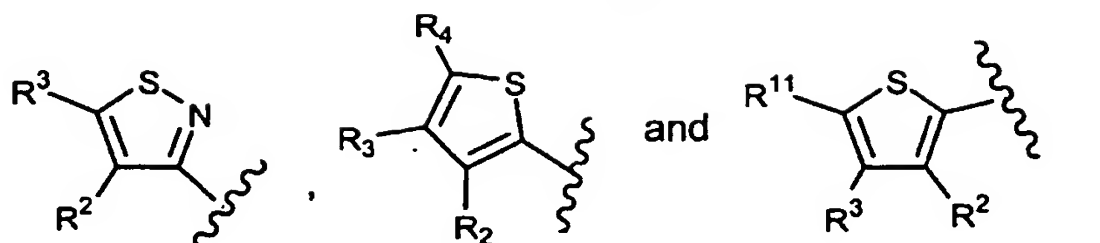


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n is 0 to 6;

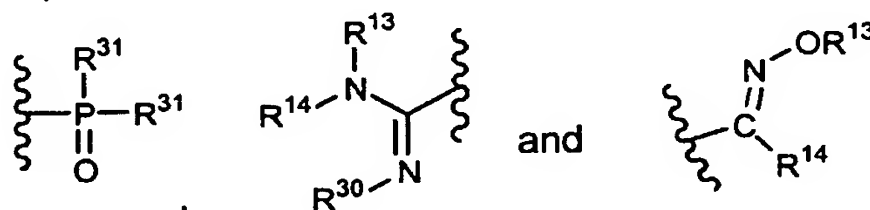
p is 1 to 5;

5 X is O, NH, or S;

Z is 1 to 3;

R^2 is selected from the group consisting of: hydrogen, OH, $-C(O)OH$, $-SH$, $-SO_2NR^{13}R^{14}$, $-NHC(O)R^{13}$, $-NHSO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, $-NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, $-C(O)NHOR^{13}$, $-C(O)NR^{13}OH$, $-S(O_2)OH$, $-OC(O)R^{13}$, an unsubstituted heterocyclic acidic functional group, and a substituted heterocyclic acidic functional group; wherein there are 1 to 6 substituents on said substituted heterocyclic acidic functional group each substituent being independently selected from the group consisting of: R^9 groups;

15 each R^3 and R^4 is independently selected from the group consisting of: hydrogen, cyano, halogen, alkyl, alkoxy, $-OH$, $-CF_3$, $-OCF_3$, $-NO_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NHR^{17}$, $-C(O)NR^{13}R^{14}$, $-SO_{(t)}NR^{13}R^{14}$, $-SO_{(t)}R^{13}$, $-C(O)NR^{13}OR^{14}$, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl,



20 wherein there are 1 to 6 substituents on said substituted aryl group and each substituent is independently selected from the group consisting of: R^9 groups; and wherein there are 1 to 6 substituents on said substituted heteroaryl group and each substituent is independently selected from the group consisting of: R^9 groups;

25 each R^5 and R^6 are the same or different and are independently selected from the group consisting of hydrogen, halogen, alkyl, alkoxy, $-CF_3$, $-OCF_3$, $-NO_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-SO_{(t)}NR^{13}R^{14}$, $-C(O)NR^{13}OR^{14}$, cyano, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl group; wherein there are 1 to 6 substituents on said substituted aryl group and each substituent is independently selected from the group consisting of: R^9 groups; and

wherein there are 1 to 6 substituents on said substituted heteroaryl group and each substituent is independently selected from the group consisting of: R^9 groups;

each R^7 and R^8 is independently selected from the group consisting of: H, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkylalkyl, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, alkynyl, alkenyl, and cycloalkenyl; and wherein there are one or more substituents on said substituted R^7 and R^8 groups, wherein each substituent is independently selected from the group consisting of:

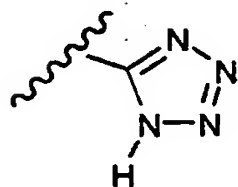
- a) halogen,
- b) $-CF_3$,
- c) $-COR^{13}$,
- d) $-OR^{13}$,
- 15 e) $-NR^{13}R^{14}$,
- f) $-NO_2$,
- g) $-CN$,
- h) $-SO_2OR^{13}$,
- i) $-Si(alkyl)_3$, wherein each alkyl is independently selected,
- 20 j) $-Si(aryl)_3$, wherein each alkyl is independently selected,
- k) $-(R^{13})_2R^{14}Si$, wherein each R^{13} is independently selected,
- l) $-CO_2R^{13}$,
- m) $-C(O)NR^{13}R^{14}$,
- n) $-SO_2NR^{13}R^{14}$,
- 25 o) $-SO_2R^{13}$,
- p) $-OC(O)R^{13}$,
- q) $-OC(O)NR^{13}R^{14}$,
- r) $-NR^{13}C(O)R^{14}$, and
- s) $-NR^{13}CO_2R^{14}$;

30 (fluoroalkyl is one non-limiting example of an alkyl group that is substituted with halogen);

R^{8a} is selected from the group consisting of: hydrogen, alkyl, cycloalkyl and cycloalkylalkyl;

each R^9 is independently selected from the group consisting of:

- a) $-R^{13}$,
 b) halogen,
 c) $-CF_3$,
 d) $-COR^{13}$,
 e) $-OR^{13}$,
 f) $-NR^{13}R^{14}$,
 g) $-NO_2$,
 h) $-CN$,
 i) $-SO_2R^{13}$,
 j) $-SO_2NR^{13}R^{14}$,
 k) $-NR^{13}COR^{14}$,
 l) $-CONR^{13}R^{14}$,
 m) $-NR^{13}CO_2R^{14}$,
 n) $-CO_2R^{13}$,
 o)



- p) alkyl substituted with one or more $-OH$ groups,
 q) alkyl substituted with one or more $-NR^{13}R^{14}$ group, and
 r) $-N(R^{13})SO_2R^{14}$;

each R^{10} and R^{11} is independently selected from the group consisting of R^{13} , halogen, $-CF_3$, $-OCF_3$, $-NR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, $-OH$, $-C(O)OR^{13}$, $-SH$, $-SO_2NR^{13}R^{14}$, $-SO_2R^{13}$, $-NHC(O)R^{13}$, $-NHCO_2NR^{13}R^{14}$, $-NHCO_2R^{13}$, $-C(O)NR^{13}R^{14}$, $-C(O)NR^{13}OR^{14}$, $-OC(O)R^{13}$ and cyano;

R^{12} is selected from the group consisting of: hydrogen, $-C(O)OR^{13}$, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkylalkyl, and unsubstituted or substituted heteroarylalkyl group; wherein there are 1 to 6 substituents on the substituted R^{12} groups and each substituent is independently selected from the group consisting of: R^9 groups;

each R^{13} and R^{14} is independently selected from the group consisting of: H, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or

substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkylalkyl, unsubstituted or substituted heterocyclic, unsubstituted or substituted fluoroalkyl, and unsubstituted or substituted heterocycloalkylalkyl (wherein "heterocycloalkyl" means heterocyclic); wherein there are 1 to 6 substituents on said substituted R^{13} and R^{14} groups and each substituent is independently selected from the group consisting of: alkyl, $-CF_3$, $-OH$, alkoxy, aryl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, $-N(R^{40})_2$, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-S(O)_iNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ provided that R^{15} is not H, halogen, and $-NHC(O)NR^{15}R^{16}$; or

R^{13} and R^{14} taken together with the nitrogen they are attached to in the groups $-C(O)NR^{13}R^{14}$ and $-SO_2NR^{13}R^{14}$ form an unsubstituted or substituted saturated heterocyclic ring (preferably a 3 to 7 membered heterocyclic ring), said ring optionally containing one additional heteroatom selected from the group consisting of: O, S and NR^{18} ; wherein there are 1 to 3 substituents on the substituted cyclized R^{13} and R^{14} groups and each substituent is independently selected from the group consisting of: alkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-SO_iNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ provided that R^{15} is not H, $-NHC(O)NR^{15}R^{16}$, $-NHC(O)OR^{15}$, halogen, and a heterocycloalkenyl group;

each R^{15} and R^{16} is independently selected from the group consisting of: H, alkyl, aryl, arylalkyl, cycloalkyl and heteroaryl;

R^{17} is selected from the group consisting of: $-SO_2$ alkyl, $-SO_2$ aryl, $-SO_2$ cycloalkyl, and $-SO_2$ heteroaryl;

R^{18} is selected from the group consisting of: H, alkyl, aryl, heteroaryl, $-C(O)R^{19}$, $-SO_2R^{19}$ and $-C(O)NR^{19}R^{20}$;

each R^{19} and R^{20} is independently selected from the group consisting of: alkyl, aryl and heteroaryl;

R^{30} is selected from the group consisting of: alkyl, cycloalkyl, $-CN$, $-NO_2$, or $-SO_2R^{15}$ provided that R^{15} is not H;

each R^{31} is independently selected from the group consisting of: unsubstituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl and unsubstituted or substituted cycloalkyl; wherein there are 1 to 6

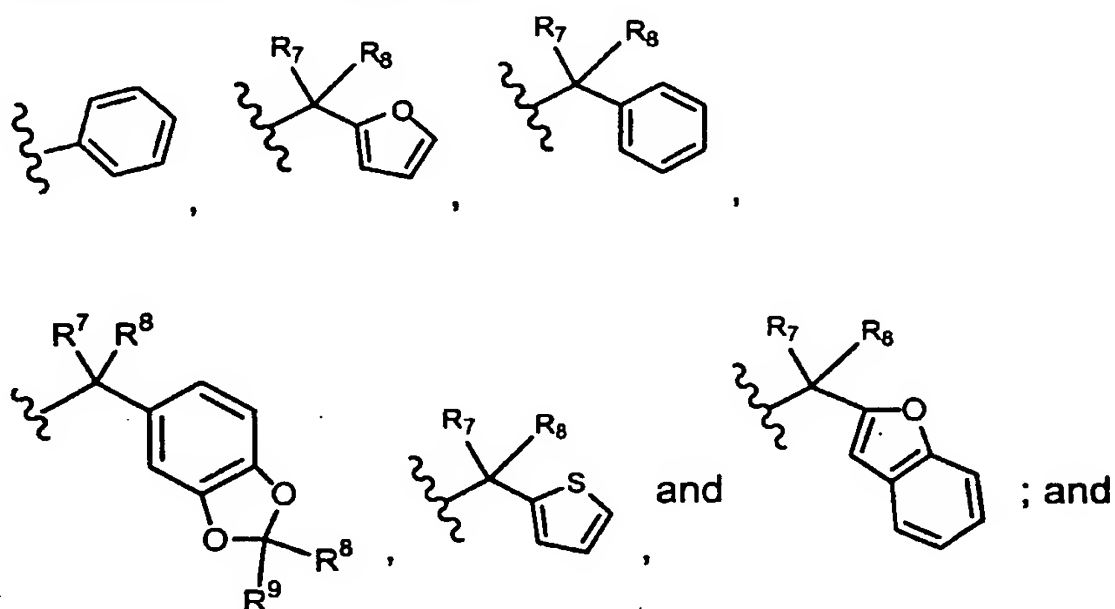
substituents on said substituted R^{31} groups and each substituent is independently selected from the group consisting of: alkyl, halogen and $-CF_3$;

each R^{40} is independently selected from the group consisting of: H, alkyl and cycloalkyl; and

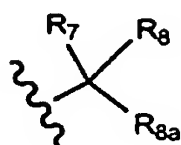
t is 0, 1 or 2.

2. The compound of claim 1 wherein A is selected from the group consisting of:

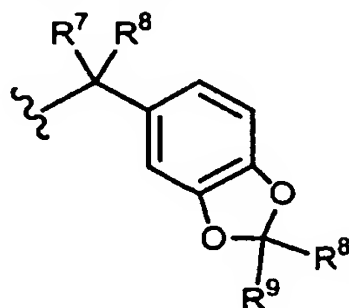
(1) unsubstituted or substituted:



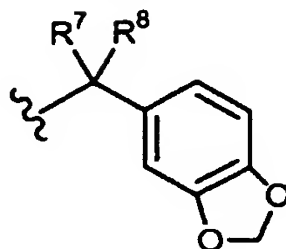
(2)



3. The compound of Claim 1 wherein A is:

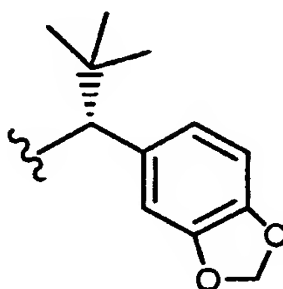


- 196
4. The compound of Claim 1 wherein A is:

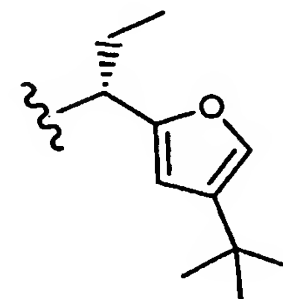
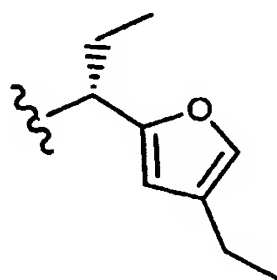
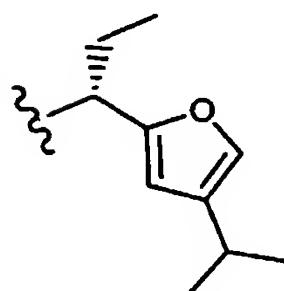
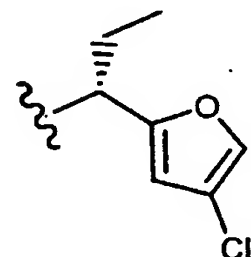
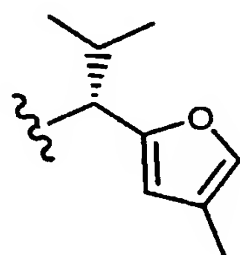
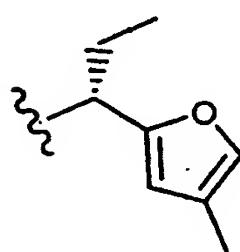
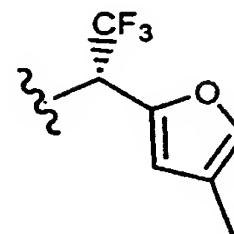
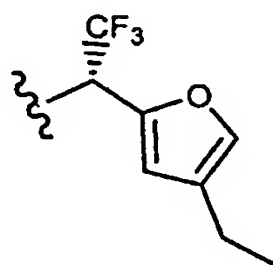
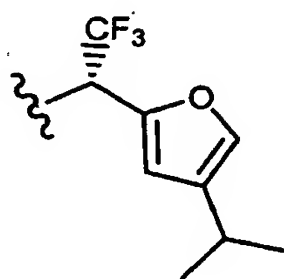


and R⁷ is H, and R⁸ is alkyl.

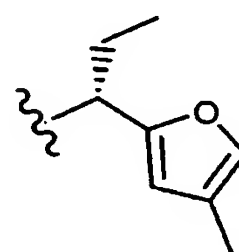
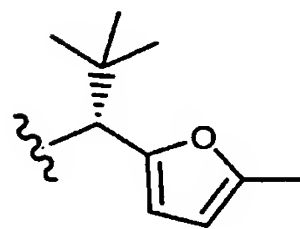
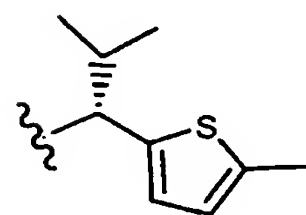
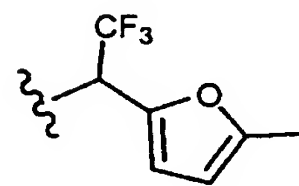
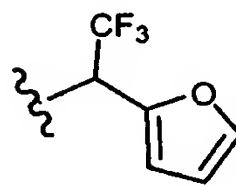
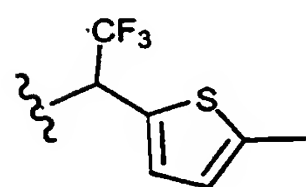
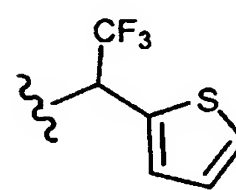
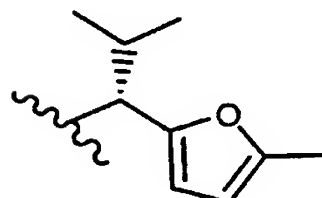
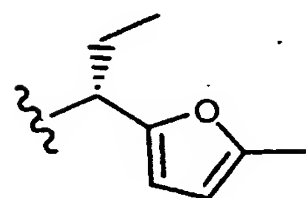
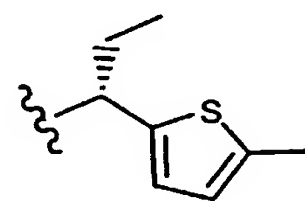
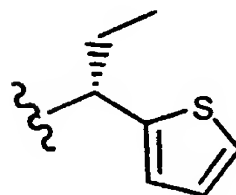
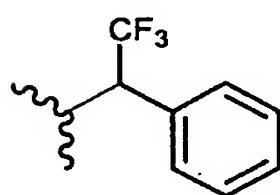
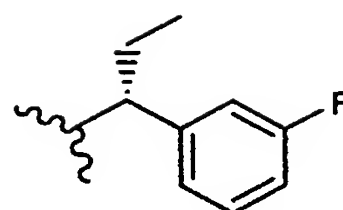
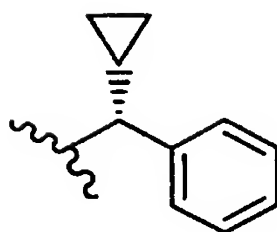
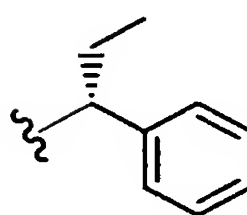
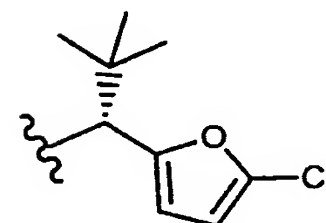
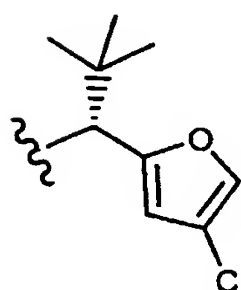
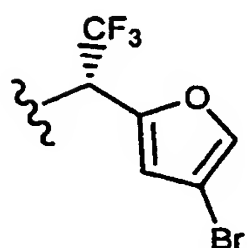
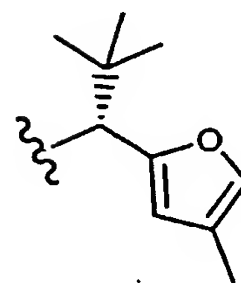
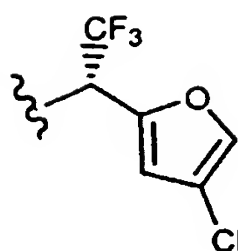
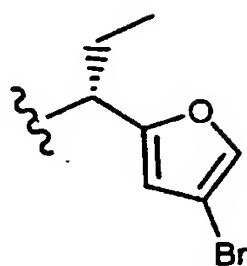
- 5 5. The compound of Claim 1 wherein A is:



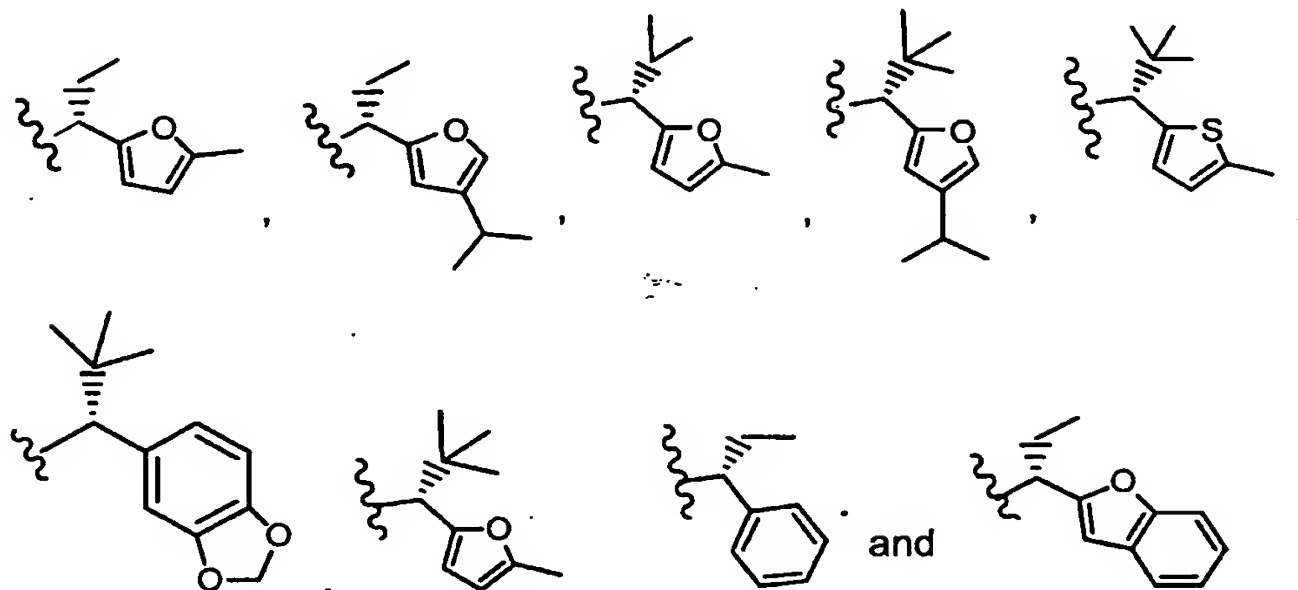
6. The compound of Claim 1 wherein A is selected from the group consisting of:



197

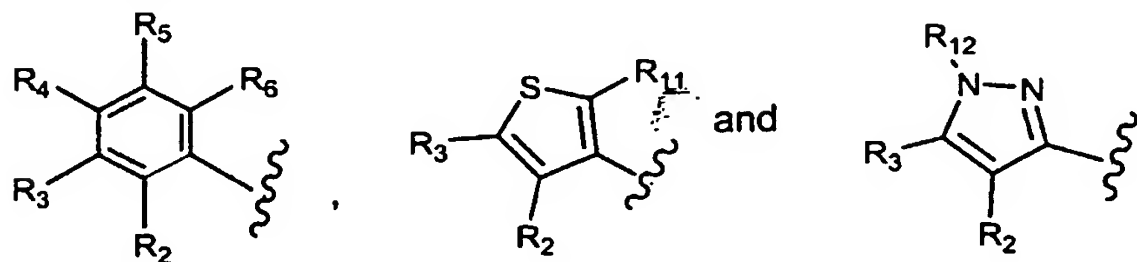


7. The compound of claim 1 wherein A is selected from the group consisting of:



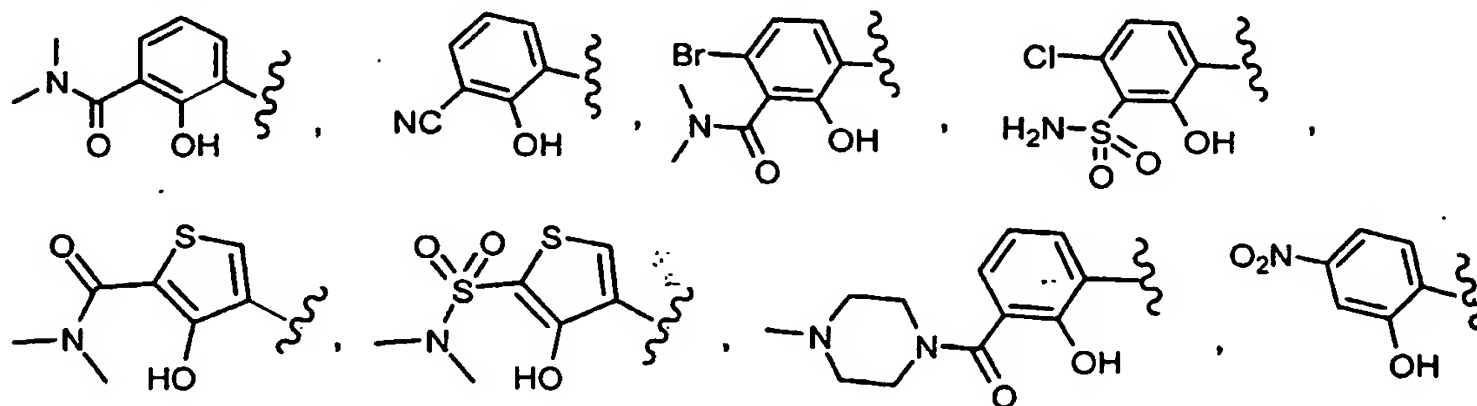
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8. The compound of Claim 1 wherein B is selected from the group consisting of:



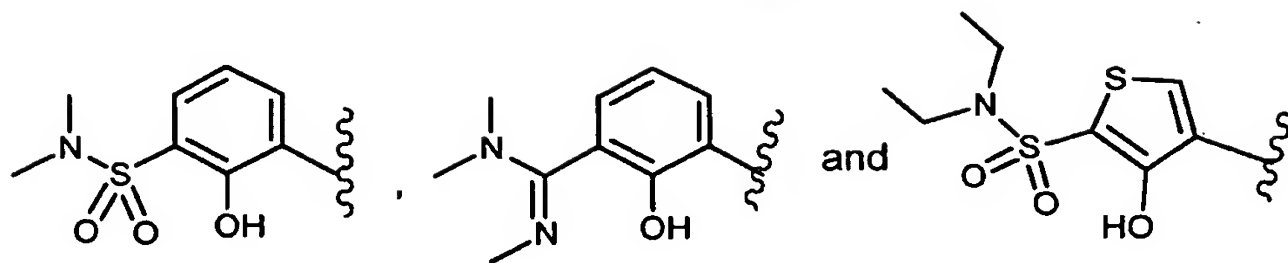
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9. The compound of Claim 1 wherein B is selected from the group consisting of:

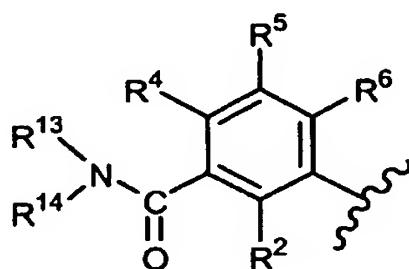


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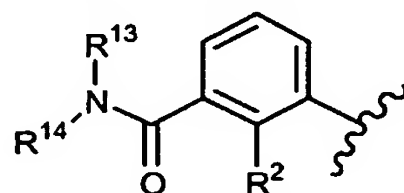


10. The compound of Claim 1 wherein B is



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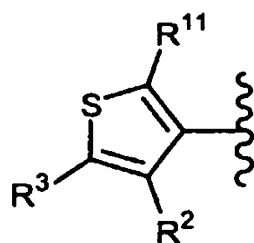
- 11. The compound of Claim 1 wherein B is:**



wherein R² is—OH, and R¹³ and R¹⁴ are independently selected from the group consisting of H and alkyl.

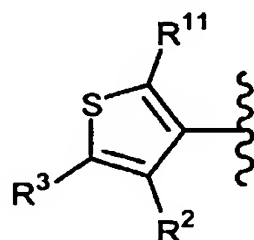
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- 12. The compound of Claim 1 wherein B is**



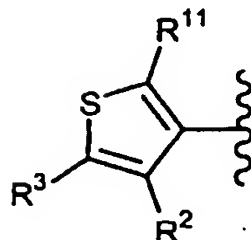
wherein R^{11} is H.

- 13. The compound of Claim 1 wherein B is:**



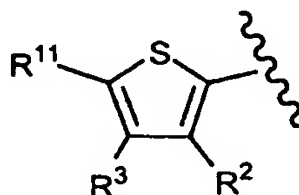
wherein R^2 is $-OH$, R^3 is $-C(O)NR^{13}R^{14}$, and R^{11} is H .

- 201
14. The compound of Claim 1 wherein B is:



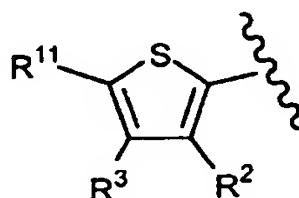
wherein R² is -OH, R³ is -S(O)_tNR¹³R¹⁴, and R¹¹ is H.

- 5 15. The compound of claim 1 wherein B is:



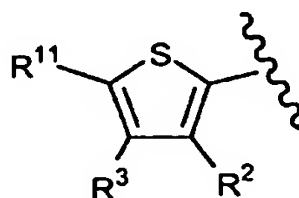
wherein R¹¹ is H.

16. The compound of Claim 1 wherein B is:



10 wherein R² is -OH, R³ is -C(O)NR¹³R¹⁴, and R¹¹ is H.

17. The compound of Claim 1 wherein B is:



15 wherein R² is -OH, R³ is -S(O)_tNR¹³R¹⁴, and R¹¹ is H.

18. The compound of Claim 1 wherein R¹ is selected from the group consisting of: H, alkyl, aryl and cycloalkyl.

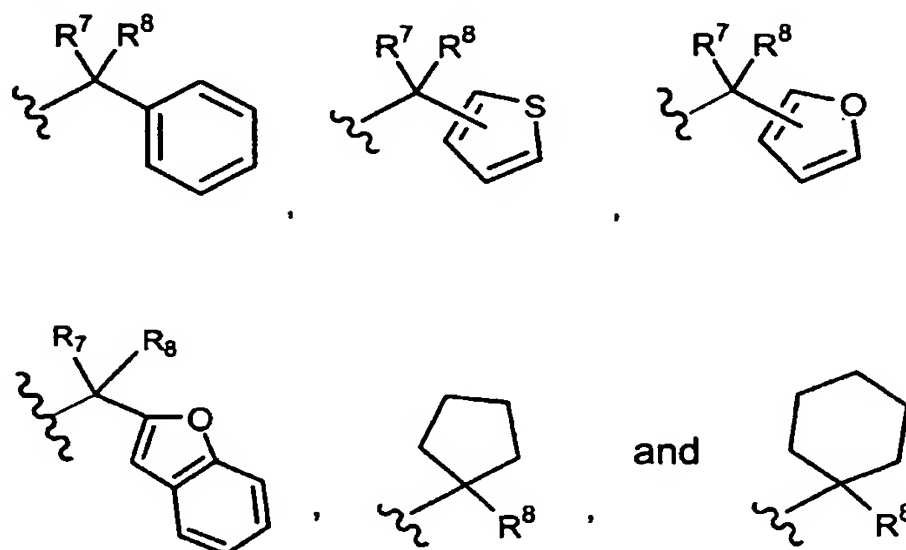
- 20 19. The compound of Claim 1 wherein: R¹ is selected from H, methyl, phenyl and cyclohexyl.

202

20. The compound of Claim 1 wherein

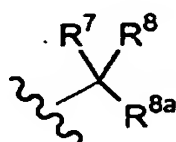
(1) substituent A in formula I is selected from the group consisting of:

(a)



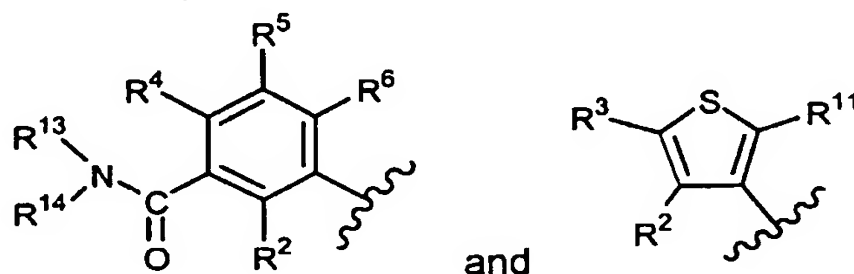
wherein the above rings are unsubstituted, or the above rings are substituted with 1 to 3 substituents independently selected from the group consisting of: H, F, Cl, Br, alkyl, cycloalkyl, and $-\text{CF}_3$; R^7 is selected from the group consisting of: H, $-\text{CF}_3$, $-\text{CF}_2\text{CH}_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and

(b)



wherein R^7 is selected from the group consisting of: H, $-\text{CF}_3$, $-\text{CF}_2\text{CH}_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and R^{8a} is as defined for formula I.

(2) substituent B in formula I is selected from the group consisting of:



wherein:

R^2 is selected from the group consisting of: H, OH, $-\text{NHC}(\text{O})\text{R}^{13}$ and $-\text{NHSO}_2\text{R}^{13}$;

203

R^3 is selected from the group consisting of: $-C(O)NR^{13}R^{14}$, $-SO_2NR^{13}R^{14}$, $-NO_2$, cyano, $-SO_2R^{13}$; and $-C(O)OR^{13}$;

R^4 is selected from the group consisting of: H, $-NO_2$, cyano, $-CH_3$ or $-CF_3$;

5 R^5 is selected from the group consisting of: H, $-CF_3$, $-NO_2$, halogen and cyano; and

R^6 is selected from the group consisting of: H, alkyl and $-CF_3$;

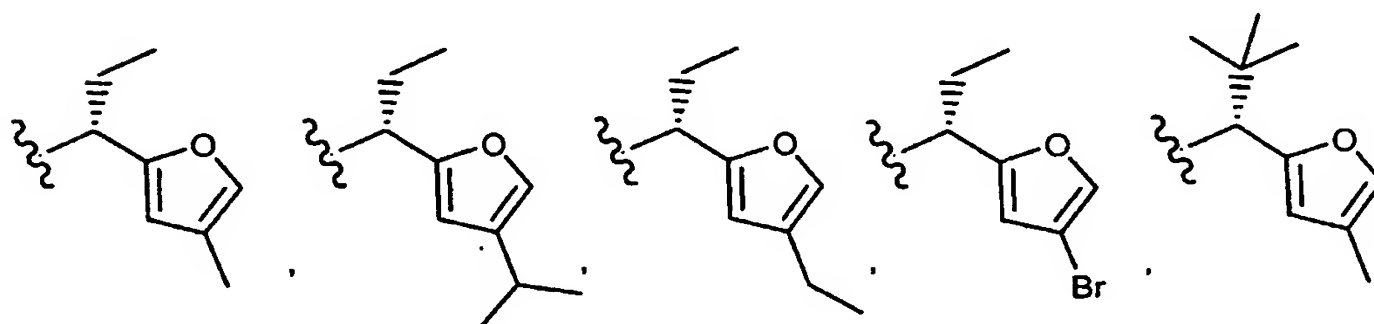
R^{11} is selected from the group consisting of: H, halogen and alkyl; and

each R^{13} and R^{14} is independently selected from the group consisting of: H, methyl, ethyl and isopropyl; or

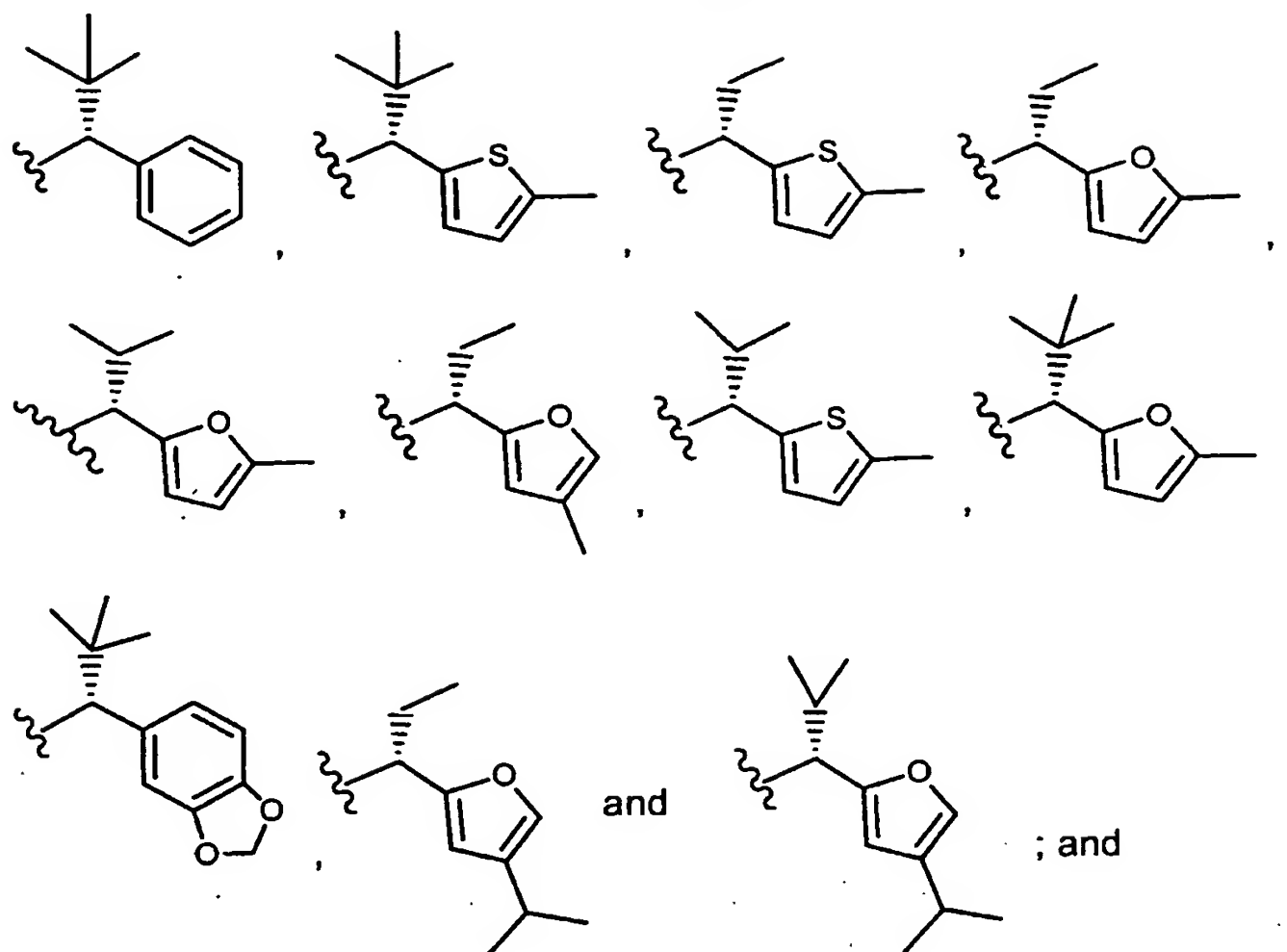
10 R^{13} and R^{14} when taken together with the nitrogen they are attached to in the groups $-NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, $-SO_2NR^{13}R^{14}$, $-OC(O)NR^{13}R^{14}$, $-CONR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, $-SO_2NR^{13}R^{14}$, $-NHCO_2NR^{13}R^{14}$ form an unsubstituted or substituted saturated heterocyclic ring (preferably a 3 to 7 membered ring) optionally having one additional heteroatom selected from O, S or NR^{18} wherein R^{18} is selected from H, alkyl, aryl, heteroaryl, $-C(O)R^{19}$, $-SO_2R^{19}$ and $-C(O)NR^{19}R^{20}$,
 15 wherein each R^{19} and R^{20} is independently selected from alkyl, aryl and heteroaryl, wherein there are 1 to 3 substituents on the substituted cyclized R^{13} and R^{14} groups and each substituent is independently selected from the group consisting of: alkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-SO_2NR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ provided that R^{15} is not H, $-NHC(O)NR^{15}R^{16}$ and halogen; and wherein each R^{15} and R^{16} is independently selected from the group consisting of: H, alkyl, aryl, arylalkyl, cycloalkyl and heteroaryl.

25 21. The compound of Claim 1 wherein:

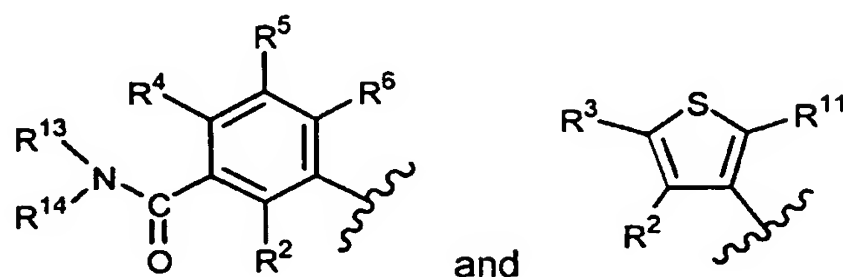
(1) substituent A in formula I is selected from the group consisting of:



204



5 (2) substituent B in formula I is selected from the group consisting of:



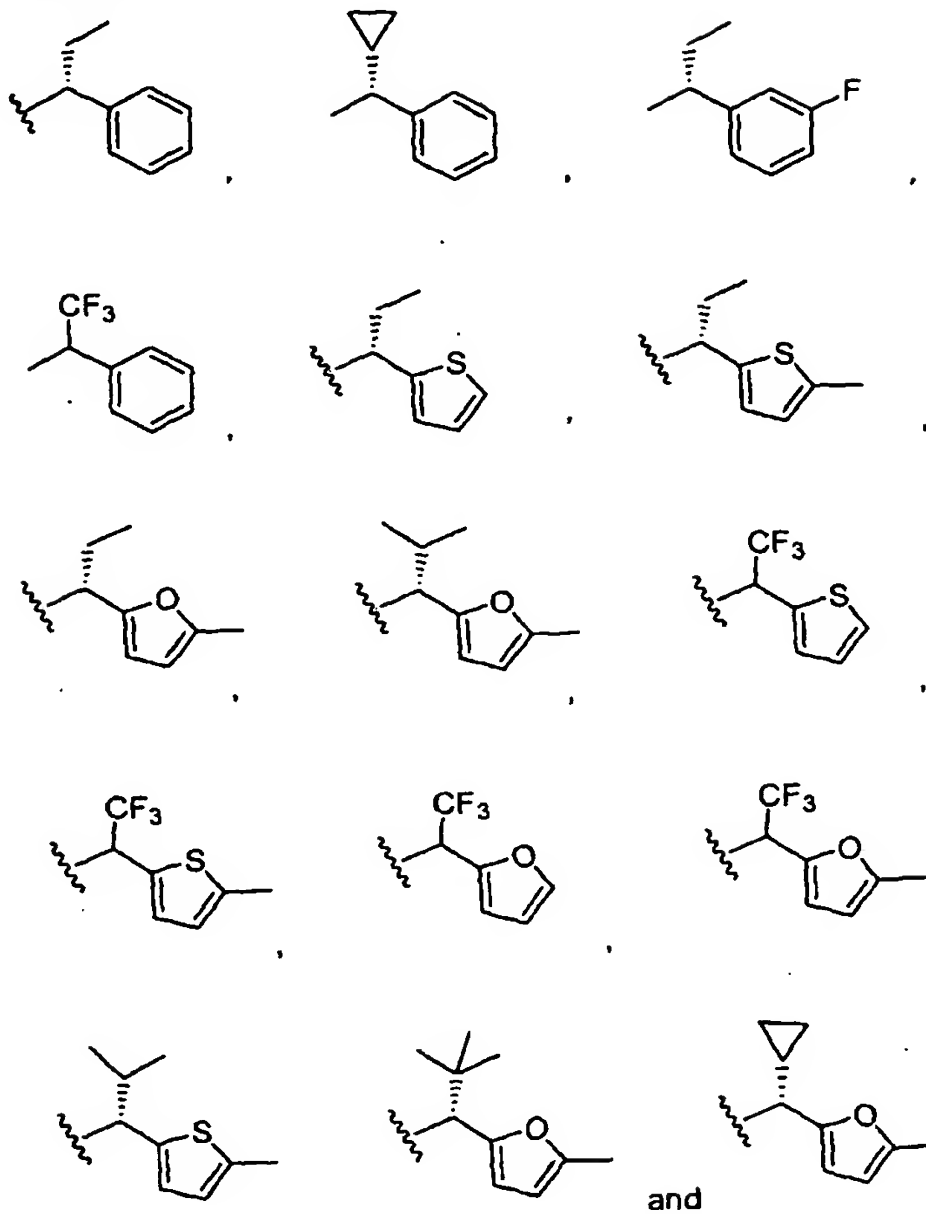
wherein:

- 10 R^2 is $-OH$;
- R^3 is selected from the group consisting of: $-SO_2NR^{13}R^{14}$ and $-CONR^{13}R^{14}$;
- R^4 is selected from the group consisting of: H , $-CH_3$ and $-CF_3$;
- R^5 is selected from the group consisting of: H and cyano;
- R^6 is selected from the group consisting of: H , $-CH_3$ and $-CF_3$;
- R^{11} is H ; and
- 15 R^{13} and R^{14} are independently selected from the group consisting of H and methyl.

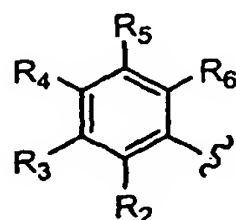
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22. The compound of Claim 1 wherein:

A is selected from:



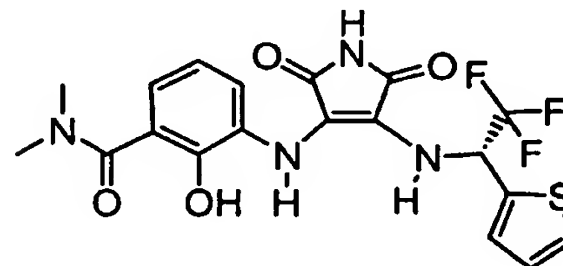
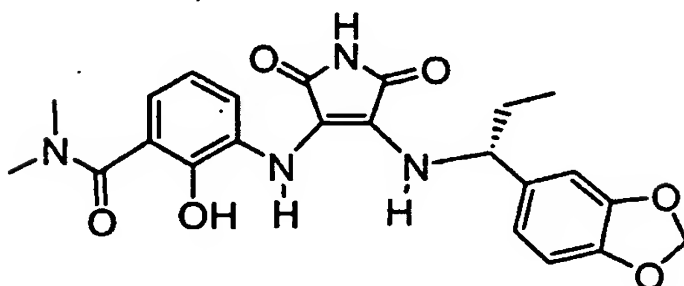
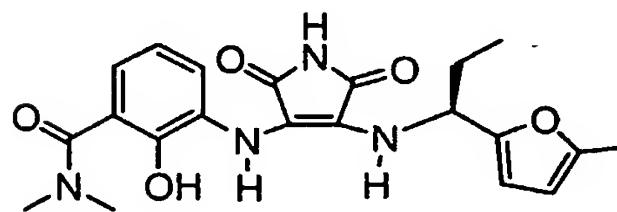
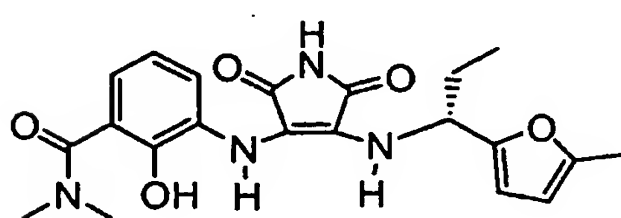
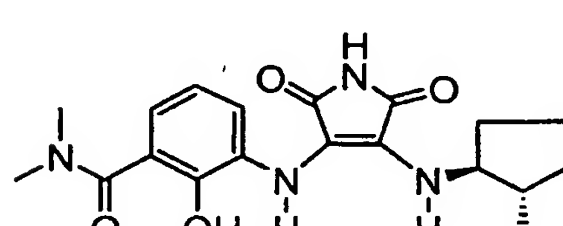
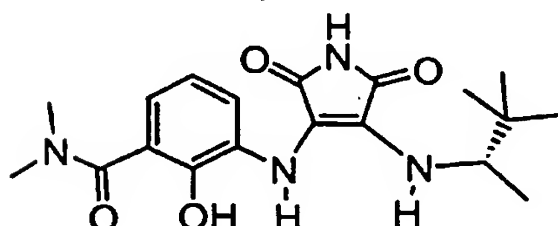
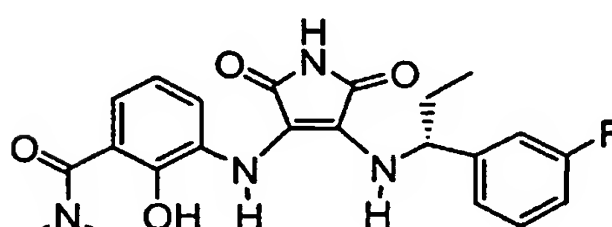
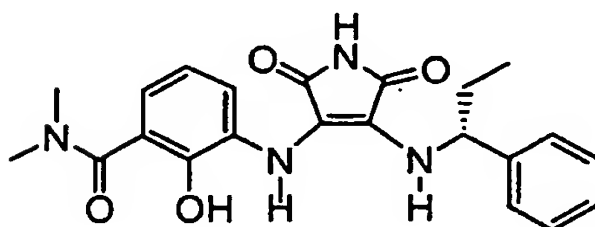
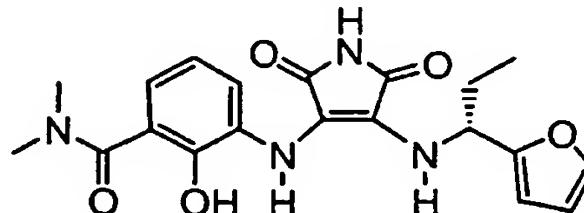
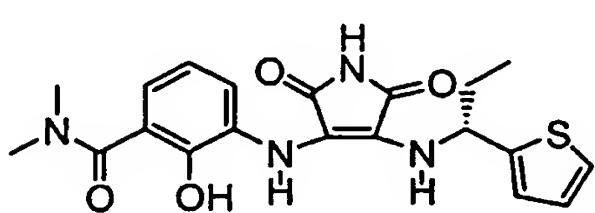
5 and B is



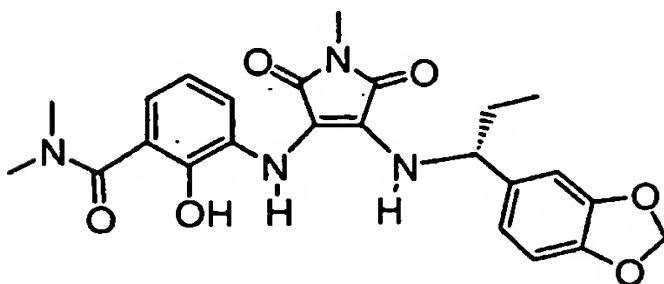
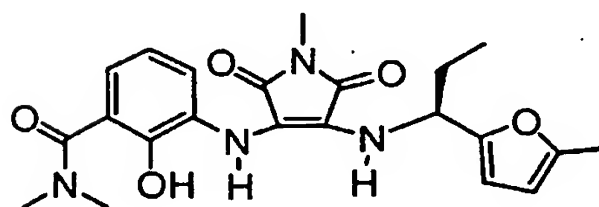
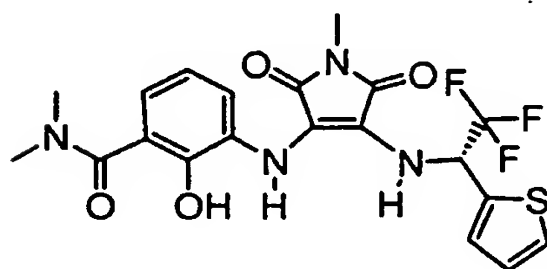
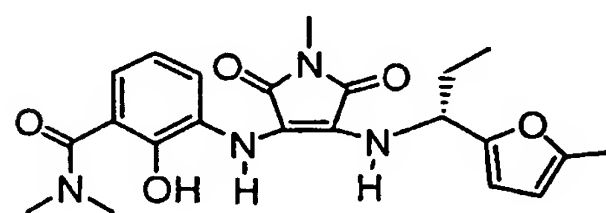
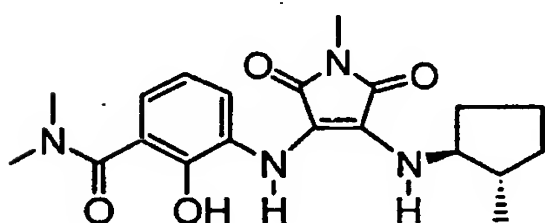
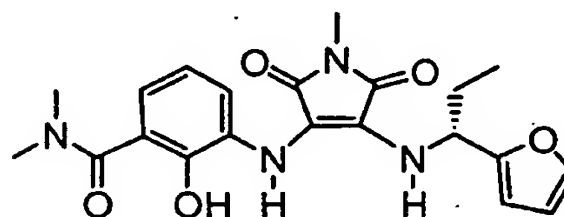
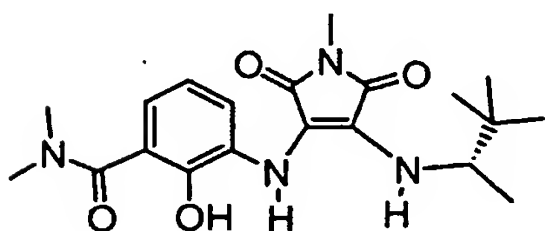
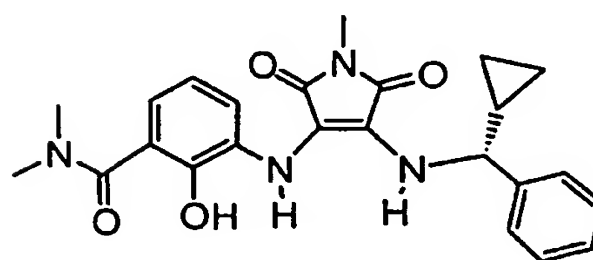
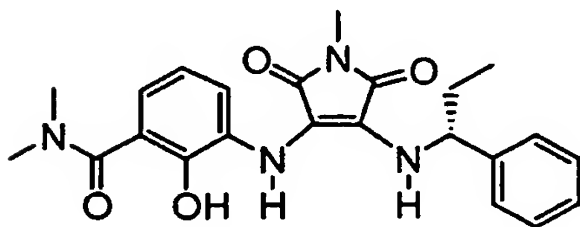
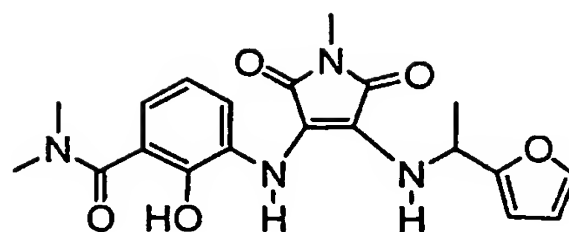
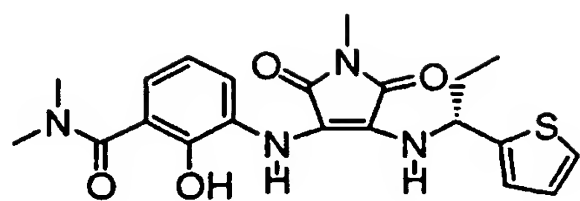
wherein,

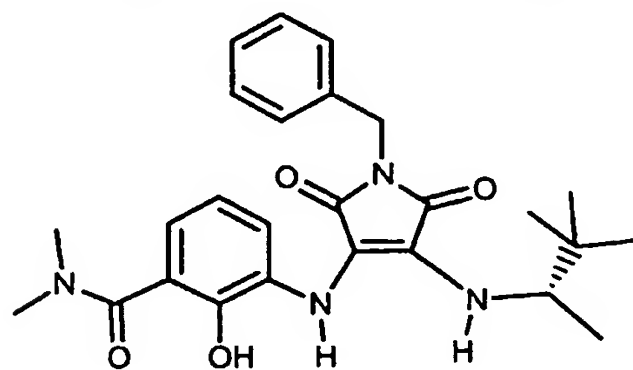
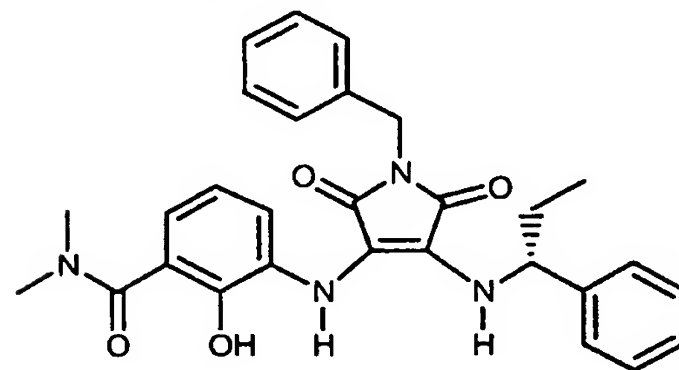
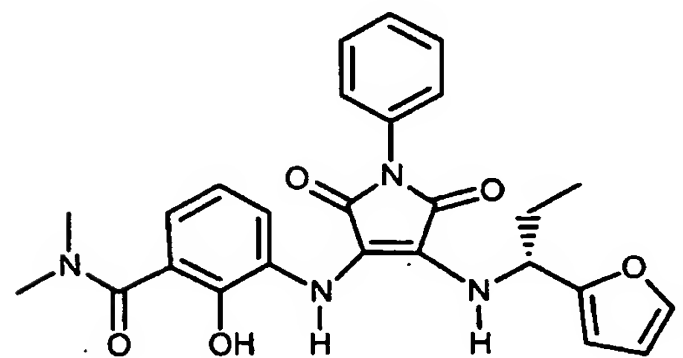
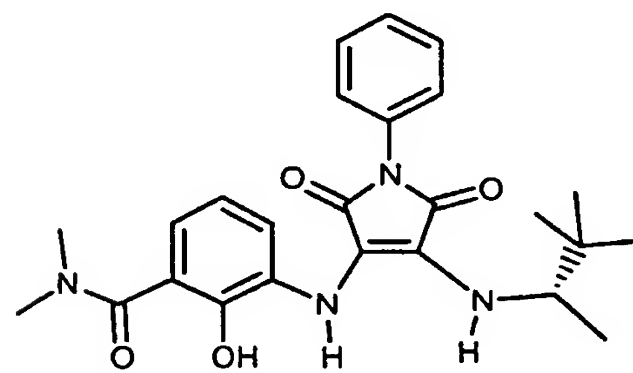
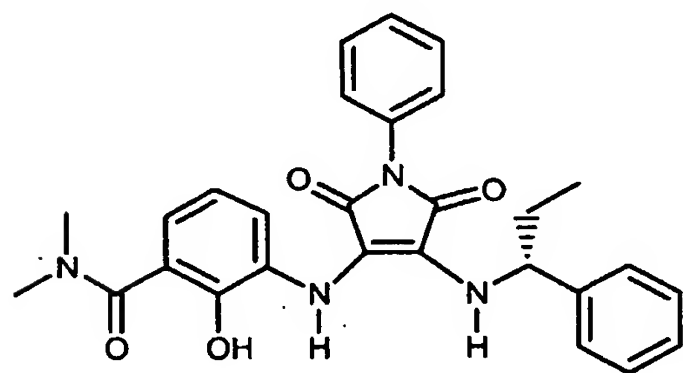
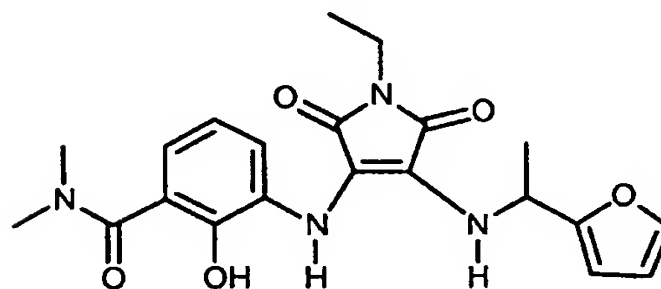
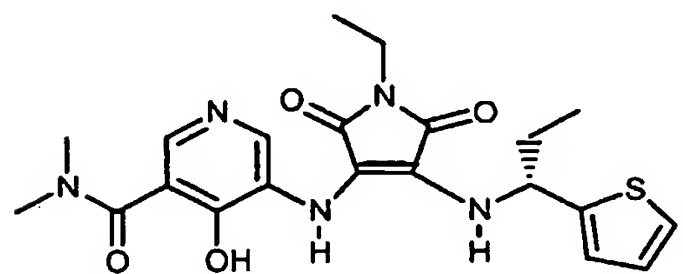
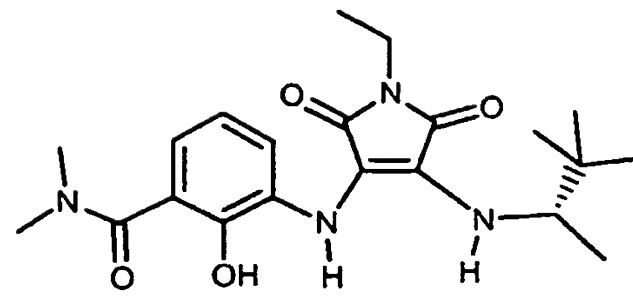
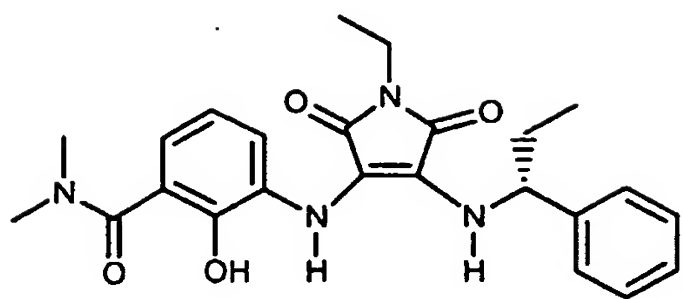
 R^2 is $-OH$; R^3 is $CONR^{13}R^{14}$;10 R^4 is selected from the group consisting of H, CF_3 and CH_3 ; R^5 is H and cyano; R^6 is selected from the group consisting of H, CH_3 and CF_3 ; R^{13} and R^{14} are methyl.

23. The compound of Claim 1 selected from the group consisting of:

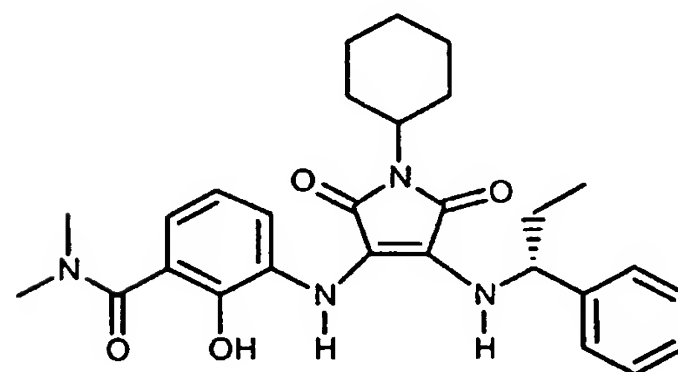


207

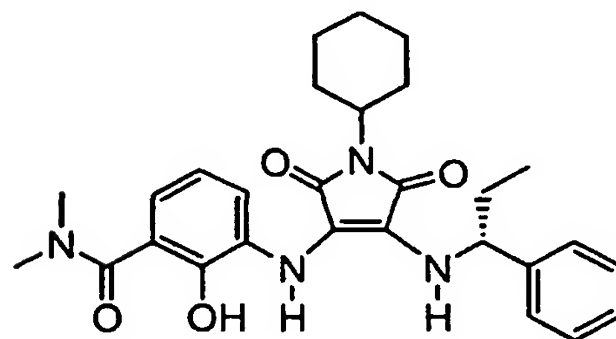
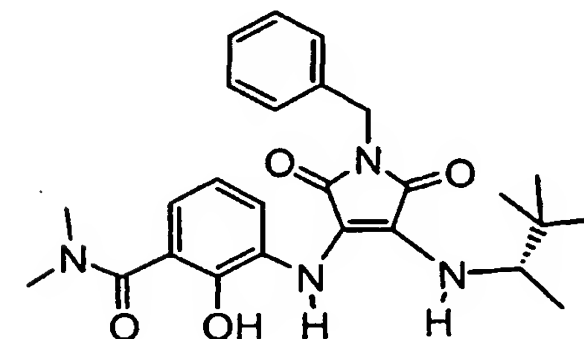
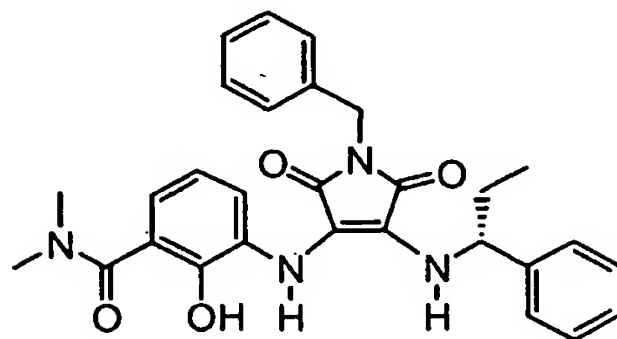
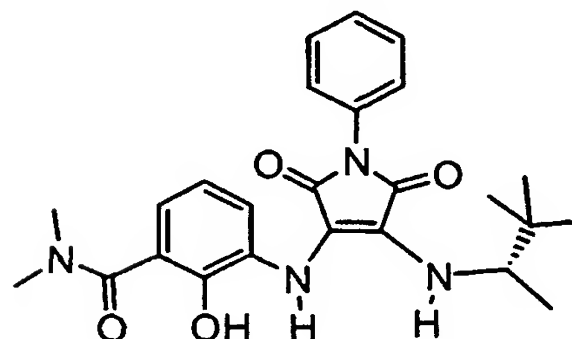
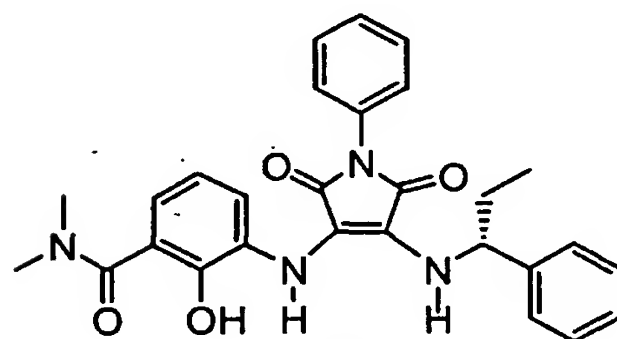
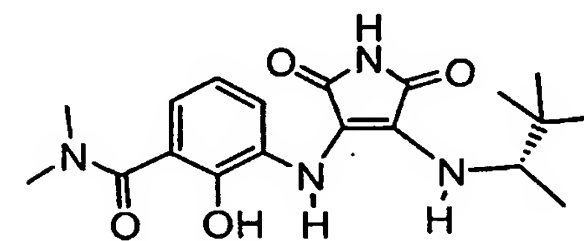
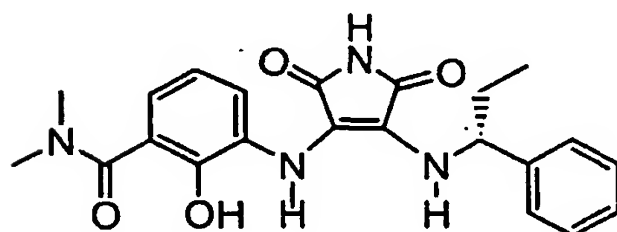
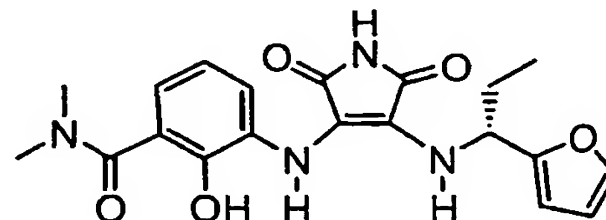
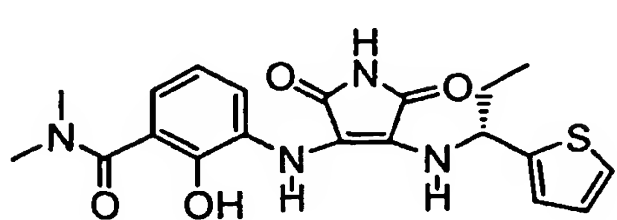




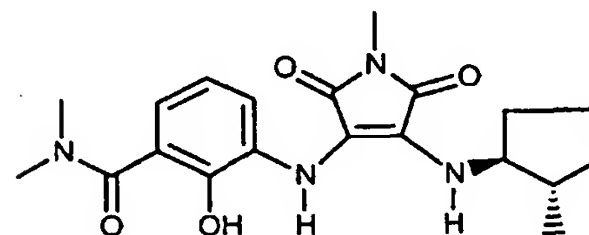
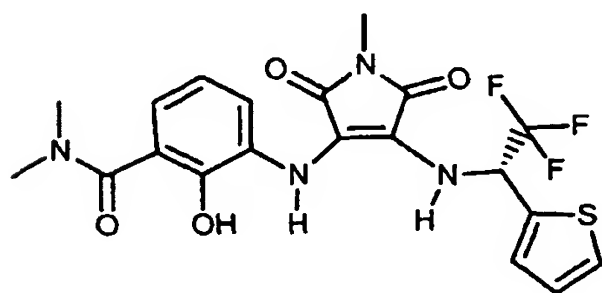
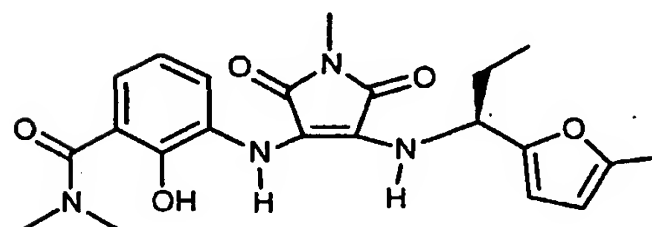
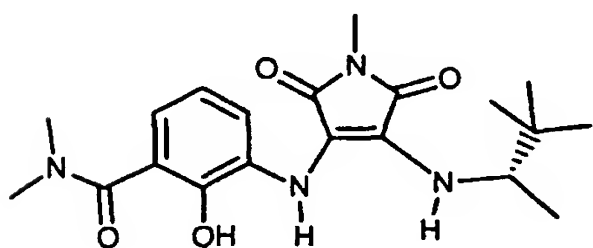
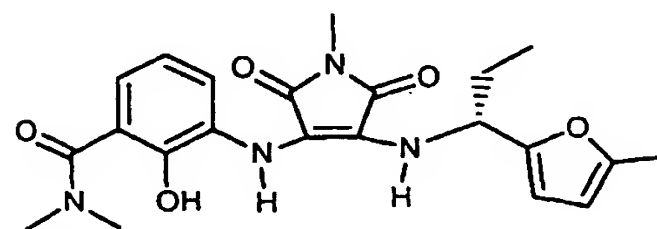
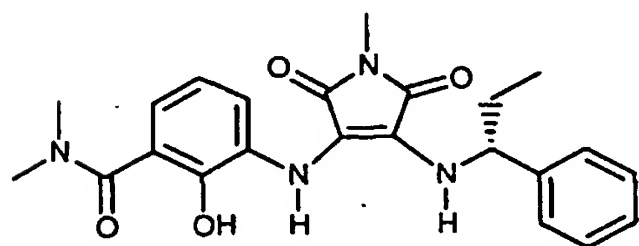
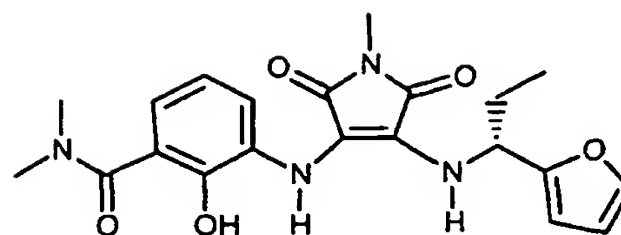
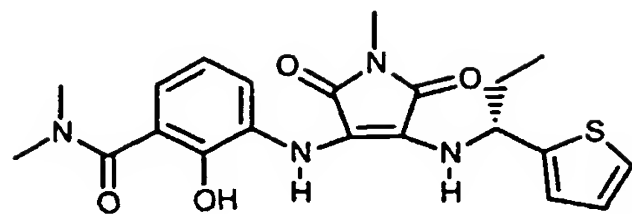
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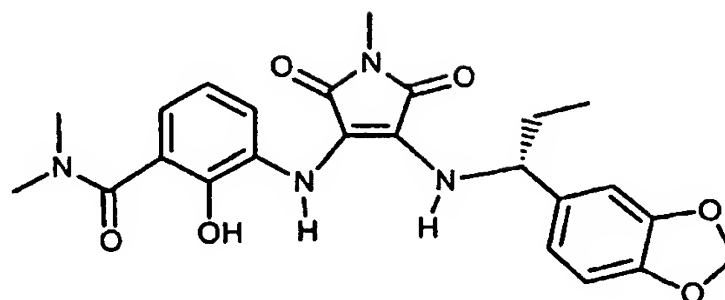
24. The compound of Claim 1 selected from the group consisting of:



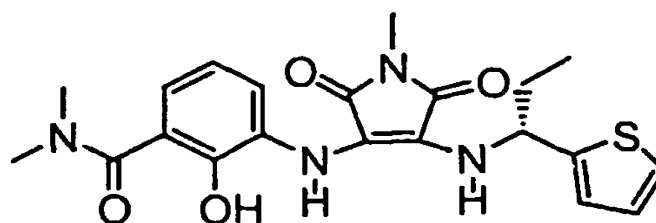
210



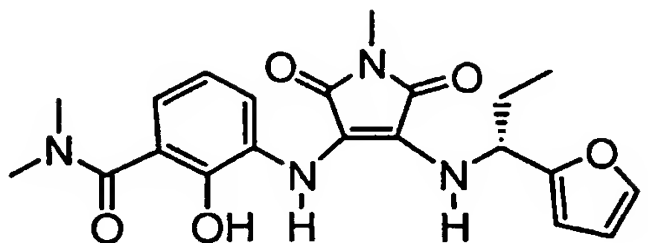
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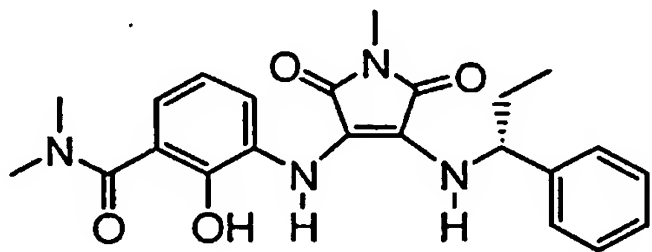
25. The compound of Claim 1 having the formula:



- 211
26. The compound of Claim 1 having the formula

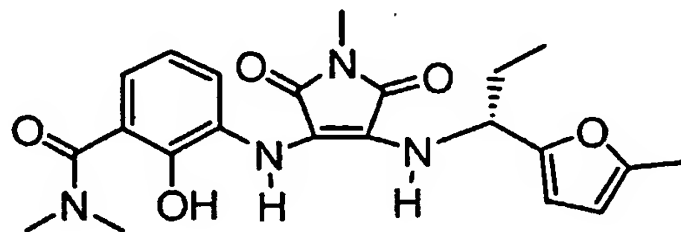


27. The compound of Claim 1 having the formula



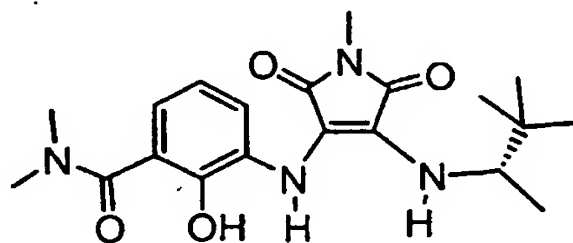
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28. The compound of Claim 1 having the formula

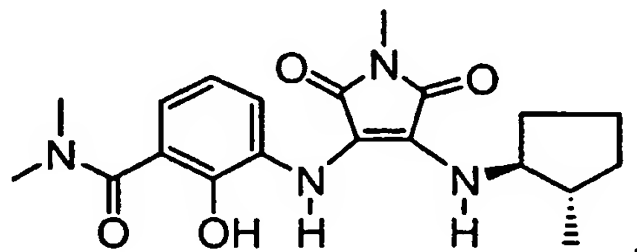


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29. The compound of Claim 1 having the formula

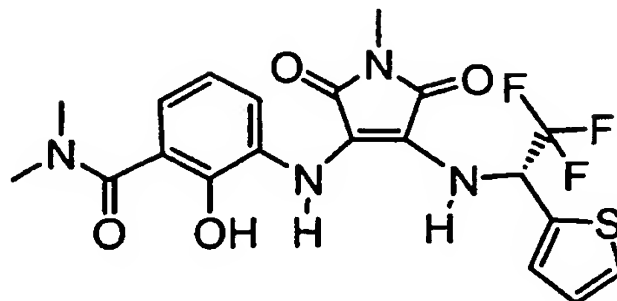


30. The compound of Claim 1 having the formula

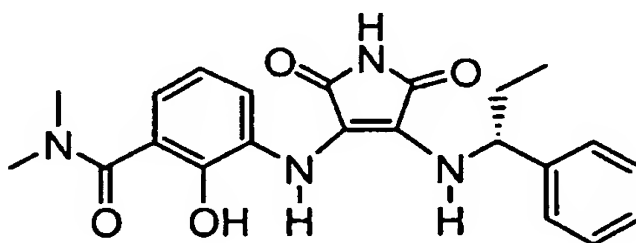


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- 212
31. The compound of Claim 1 having the formula



32. The compound of Claim 1 having the formula



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33. The compound of Claim 1 selected from the group consisting of final compounds of Examples 500 to 697 and 702 to 741.

34. A pharmaceutical composition comprising a compound of Claim 1,
and a pharmaceutically acceptable carrier therefor.

35. A method of treating a chemokine-mediated disease, wherein the chemokine binds to a CXCR2 and/or CXCR1 receptor, in a patient in need of such treatment, comprising administering to said patient a therapeutically effective amount of the compound of Claim 1, or a pharmaceutically acceptable salt or solvate thereof.

36. A method of treating a chemokine-mediated disease, wherein the chemokine binds to a CXC receptor, in a patient in need of such treatment, comprising administering to said patient a therapeutically effective amount of a compound of Claim 1.

37. The method of Claim 35 wherein said chemokine mediated disease is selected from the group consisting of: psoriasis, atopic dermatitis, asthma, COPD, adult respiratory disease, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, septic shock, endotoxic shock, gram negative sepsis, toxic shock

syndrome, stroke, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer's disease, graft vs. host reaction, allograft rejections, malaria, acute respiratory distress syndrome, delayed type hypersensitivity reaction, atherosclerosis, cerebral and cardiac ischemia, osteoarthritis, multiple sclerosis, restinosis, angiogenesis, osteoporosis, gingivitis, respiratory viruses, herpes viruses, hepatitis viruses, HIV, Kaposi's sarcoma associated virus, meningitis, cystic fibrosis, pre-term labor, cough, pruritis, multi-organ dysfunction, trauma, strains, sprains, contusions, psoriatic arthritis, herpes, encephalitis, CNS vasculitis, traumatic brain injury, CNS tumors, subarachnoid hemorrhage, post surgical trauma, interstitial pneumonitis, hypersensitivity, crystal induced arthritis, acute and chronic pancreatitis, acute alcoholic hepatitis, necrotizing enterocolitis, chronic sinusitis, angiogenic ocular disease, ocular inflammation, retinopathy of prematurity, diabetic retinopathy, macular degeneration with the wet type preferred and corneal neovascularization, polymyositis, vasculitis, acne, gastric and duodenal ulcers, celiac disease, esophagitis, glossitis, airflow obstruction, airway hyperresponsiveness, bronchiectasis, bronchiolitis, bronchiolitis obliterans, chronic bronchitis, cor pulmonae, cough, dyspnea, emphysema, hypercapnea, hyperinflation, hypoxemia, hyperoxia-induced inflammations, hypoxia, surgical lung volume reduction, pulmonary fibrosis, pulmonary hypertension, right ventricular hypertrophy, peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD), granulocytic ehrlichiosis, sarcoidosis, small airway disease, ventilation-perfusion mismatching, wheeze, colds, gout, alcoholic liver disease, lupus, burn therapy, periodontitis, transplant reperfusion injury and early transplantation.

25 38. A method of treating cancer in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of a compound of Claim 1.

30 39. A method of treating cancer in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of a compound of Claim 1, and administering a therapeutically effective amount of at least one known anti-cancer agent and/or radiation therapy.

40. The method of Claim 39, wherein said anti-cancer agent is selected from the group consisting of alkylating agents, antimetabolites, natural products and their derivatives, hormones, anti-hormones, anti-angiogenic agents and steroids (including synthetic analogs), and synthetics.

5

41. A method of inhibiting angiogenesis in a patient in need of such treatment comprising administering to said patient an angiogenesis-inhibiting amount of a compound of Claim 1.

10

42. A method of inhibiting angiogenesis in a patient in need of such treatment comprising administering to said patient an angiogenesis-inhibiting amount of a compound of Claim 1, and administering an effective amount of least one known anti-angiogenesis compound.

15

43. The method of Claim 42 wherein said known anti-angiogenesis compound is selected from the group consisting of Marimastat, AG3340, Col-3, Neovastat, BMS-275291, Thalidomide, Squalamine, Endostatin, SU-5416, SU-6668, Interferon-alpha, Anti-VEGF antibody, EMD121974, CAI, Interleukin-12, IM862, Platelet Factor-4, Vitaxin, Angiostatin, Suramin, TNP-470, PTK-787, ZD-6474, ZD-101, Bay 129566, CGS27023A, VEGF receptor kinase inhibitors, taxotere and Taxol.

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44. A method of treating a disease in a patient in need of such treatment, wherein said disease is selected from the group consisting of gingivitis, respiratory viruses, herpes viruses, hepatitis viruses, HIV, kaposi's sarcoma associated virus and atherosclerosis comprising administering to said patient a therapeutically effective amount of a compound of Claim 1.

25

45. The method of Claim 35 wherein said chemokine mediated disease is an angiogenic ocular disease.

30

46. The method of Claim 45 wherein said angiogenic ocular disease is selected from the group consisting of ocular inflammation, retinopathy of

215

prematurity, diabetic retinopathy, macular degeneration with the wet type preferred and corneal neovascularization.

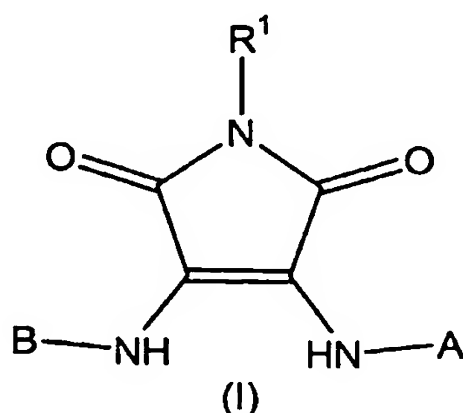
5 47. The method of Claim 41 wherein the tumor type is melanoma, gastric carcinoma or non-small cell lung carcinoma.

10 48. A method of inhibiting angiogenesis in a patient in need of such treatment comprising administering to said patient an angiogenesis-inhibiting amount of a compound of Claim 1, and administering at least one known anti-cancer agent and/or radiation therapy.

15 49. The method of Claim 48, wherein said anti-cancer agent is selected from the group consisting of alkylating agents, antimetabolites, natural products and their derivatives, hormones, anti-hormones, anti-angiogenic agents and steroids (including synthetic analogs), and synthetics.

20 50. The method of Claim 49 wherein said anti-angiogenic agent is selected from the group consisting of Marimastat, AG3340, Col-3, Neovastat, BMS-275291, Thalidomide, Squalamine, Endostatin, SU-5416, SU-6668, Interferon-alpha, Anti-VEGF antibody, EMD121974, CAI, Interleukin-12, IM862, Platelet Factor-4, Vitaxin, Angiostatin, Suramin, TNP-470, PTK-787, ZD-6474, ZD-101, Bay 129566, CGS27023A, VEGF receptor kinase inhibitors, taxotere and Taxol.

51. A compound of the formula (I):



or a pharmaceutically acceptable salt or solvate thereof, wherein:

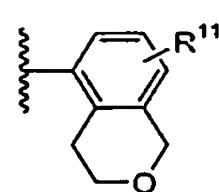
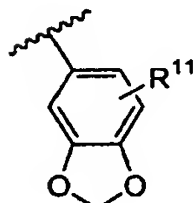
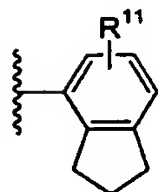
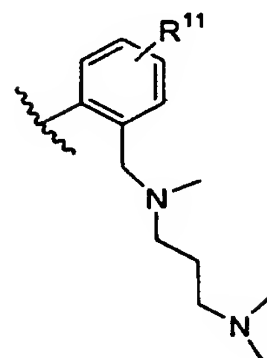
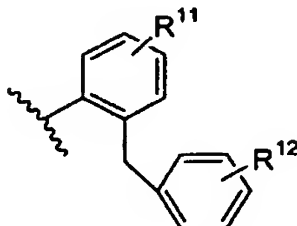
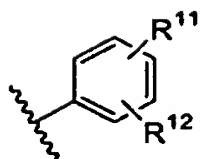
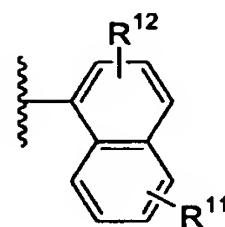
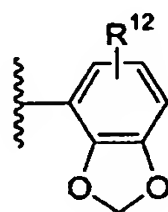
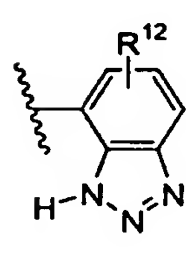
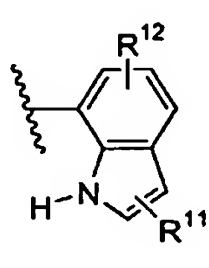
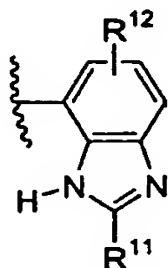
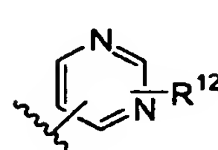
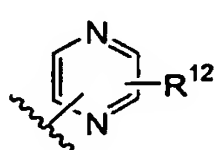
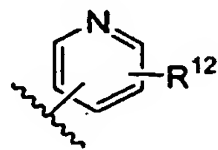
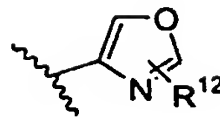
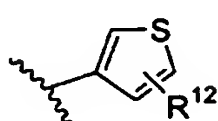
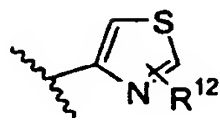
R¹ is selected from the group consisting of: H, aryl, heteroaryl, alkyl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, and

heterocycloalkylalkyl; optionally substituted with one or more substituents selected from the group consisting of:

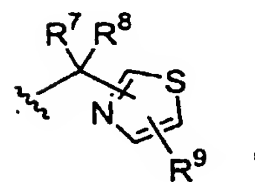
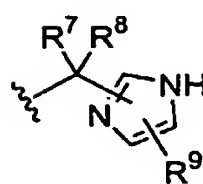
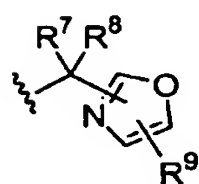
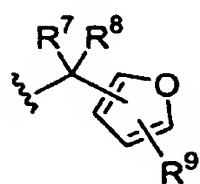
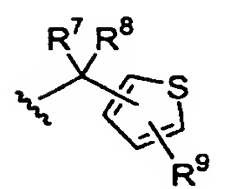
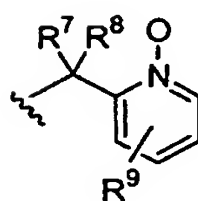
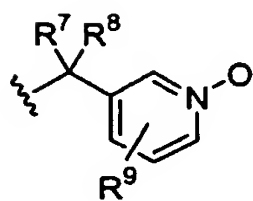
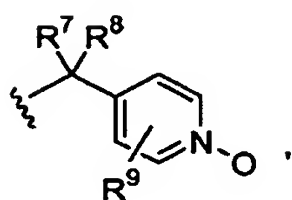
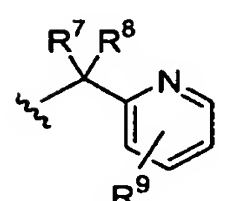
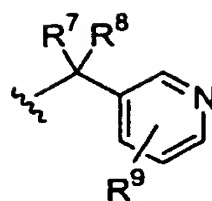
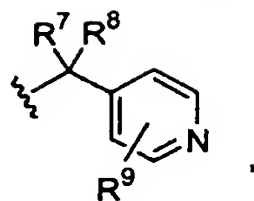
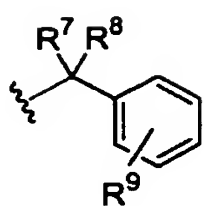
- a) H,
- b) Halogen,
- c) CF_3 ,
- d) COR^{13} ,
- e) OH,
- f) $\text{NR}^{13}\text{R}^{14}$,
- g) NO_2 ,
- h) Cyano,
- i) $-\text{Si}(\text{alkyl})$,
- j) $-\text{Si}(\text{aryl})$,
- k) $\text{SO}_2\text{OR}^{13}$,
- l) CO_2R^{13} ,
- m) $\text{CONR}^{13}\text{R}^{14}$,
- n) $\text{SO}_2\text{NR}^{13}\text{R}^{14}$,
- o) SO_2R^{13} ,
- p) $-\text{OR}^{13}$,
- r) $-\text{NR}^{13}\text{R}^{14}$,
- s) $-\text{O}(\text{C}=\text{O})\text{R}^{13}$,
- t) $-\text{O}(\text{C}=\text{O})\text{NR}^{13}\text{R}^{14}$,
- u) $-\text{NR}^{13}\text{COR}^{14}$ and
- v) $-\text{NR}^{13}\text{CO}_2\text{R}^{14}$;

217

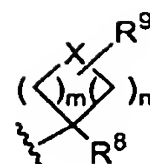
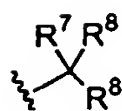
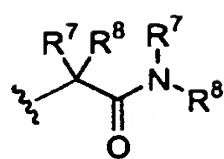
A is selected from the group consisting of:



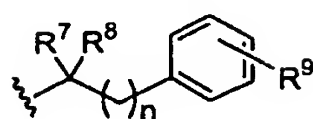
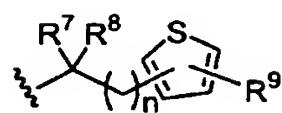
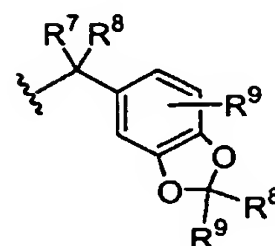
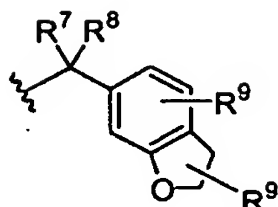
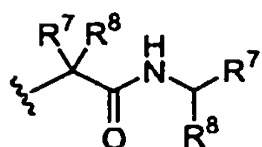
218



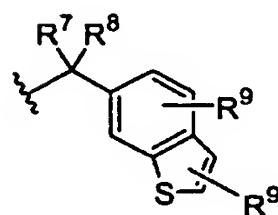
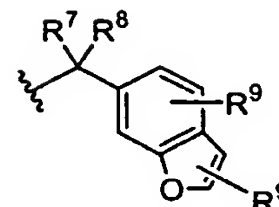
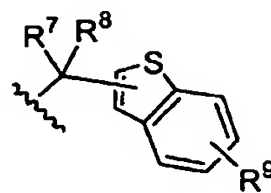
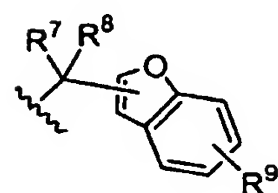
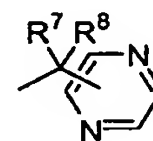
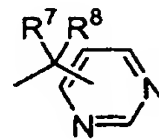
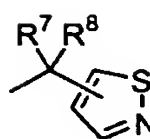
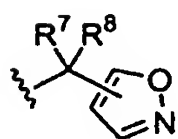
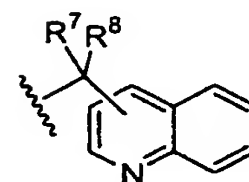
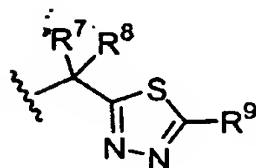
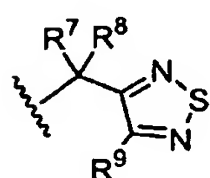
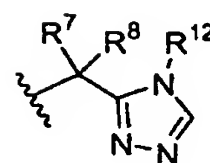
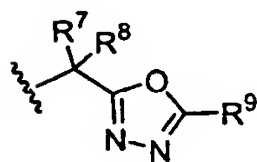
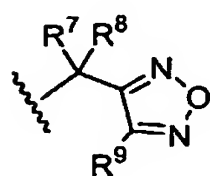
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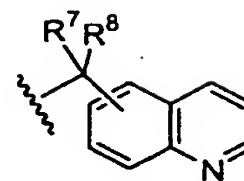
m = 1 - 5
n = 0 - 4
X = C, O, N, S



n = 0 - 6

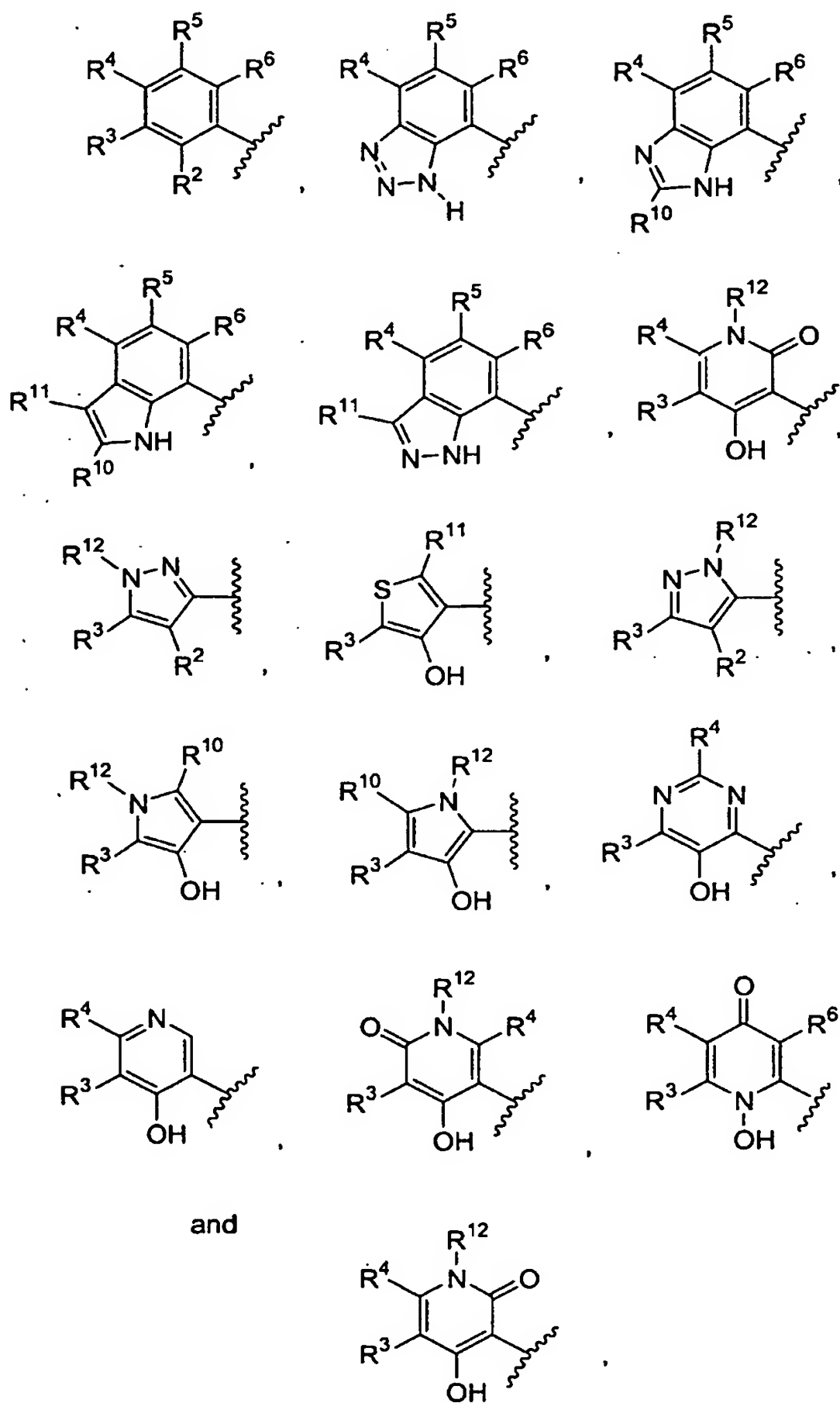


and



and

B is an optionally substituted aryl or heteroaryl group selected from the group consisting of:



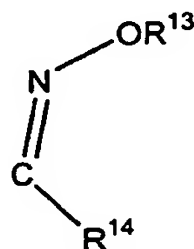
and

5 wherein,

R^2 is selected from the group consisting of hydrogen, OH, C(O)OH, SH, $\text{SO}_2\text{NR}^{13}\text{R}^{14}$, NHC(O)R^{13} , $\text{NHSO}_2\text{NR}^{13}\text{R}^{14}$, $\text{NHSO}_2\text{R}^{13}$, $\text{NR}^{13}\text{R}^{14}$, $\text{C(O)NR}^{13}\text{R}^{14}$,

$C(O)NHOR^{13}$, $C(O)NR^{13}OH$, $OC(O)R^{13}$ ²²¹ and an optionally substituted cyclic or heterocyclic acidic functional group, with the proviso that if R^2 is $SO_2NR^{13}R^{14}$, at least one of R^{13} and R^{14} must be hydrogen;

R^3 and R^4 are independently selected from the group consisting of hydrogen,
5 halogen, alkyl, alkoxy, OH, CF_3 , OCF_3 , NO_2 , $C(O)R^{13}$, $C(O)OR^{13}$, $C(O)NR^{13}R^{14}$,



$SO_{(t)}NR^{13}R^{14}$, $SO_{(t)}R^{13}$, $C(O)NR^{13}OR^{14}$, , cyano, and optionally substituted aryl or heteroaryl, wherein the substituents on said optionally substituted groups are independently selected from the group consisting of R^9 substituents.

R^5 and R^6 are independently selected from the group consisting of hydrogen,
10 halogen, alkyl, alkoxy, CF_3 , OCF_3 , NO_2 , $C(O)R^{13}$, $C(O)OR^{13}$, $C(O)NR^{13}R^{14}$,
 $SO_{(t)}NR^{13}R^{14}$, $C(O)NR^{13}OR^{14}$, cyano, and an optionally substituted aryl or heteroaryl group, wherein the substituents on said optionally substituted groups are independently selected from the group consisting of R^9 substituents;

R^7 and R^8 are the same or different and are independently selected from the
15 group consisting of H; optionally substituted or unsubstituted alkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, CO_2R^{13} , $CONR^{13}R^{14}$, fluoroalkyl, alkynyl, alkenyl, alkynylalkyl, alkenylalkyl, and cycloalkenyl, wherein said substituents on said substituted groups are selected from the group consisting of:

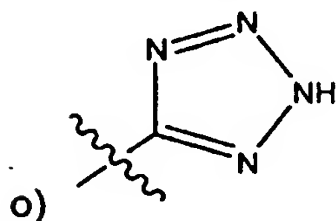
- 20 a) H,
b) Halogen,
c) CF_3 ,
d) COR^{13} ,
e) OH,
25 f) $NR^{13}R^{14}$,
g) NO_2 ,
h) Cyano,
i) $-Si(\text{alkyl})$,
j) $-Si(\text{aryl})$,
30 k) SO_2OR^{13} ,

222

- l) CO_2R^{13} ,
- m) $\text{CONR}^{13}\text{R}^{14}$,
- n) $\text{SO}_2\text{NR}^{13}\text{R}^{14}$,
- o) SO_2R^{13} ,
- p) $-\text{OR}^{13}$,
- r) $-\text{NR}^{13}\text{R}^{14}$,
- s) $-\text{O}(\text{C}=\text{O})\text{R}^{13}$,
- t) $-\text{O}(\text{C}=\text{O})\text{NR}^{13}\text{R}^{14}$,
- u) $-\text{NR}^{13}\text{COR}^{14}$ and
- v) $-\text{NR}^{13}\text{CO}_2\text{R}^{14}$;

Each R^9 is independently selected from the group consisting of:

- a) R^{13} ;
- b) halogen;
- c) $-\text{CF}_3$;
- d) $-\text{COR}^{13}$;
- e) $-\text{OR}^{13}$;
- f) $-\text{NR}^{13}\text{R}^{14}$;
- g) $-\text{NO}_2$;
- h) $-\text{CN}$;
- i) $-\text{SO}_2\text{R}^{13}$;
- j) $-\text{SO}_2\text{NR}^{13}\text{R}^{14}$;
- k) $-\text{NR}^{13}\text{COR}^{14}$;
- l) $-\text{CONR}^{13}\text{R}^{14}$;
- m) $-\text{NR}^{13}\text{CO}_2\text{R}^{14}$;
- n) CO_2R^{13} , and



R^{10} and R^{11} are independently selected from the group consisting of hydrogen, halogen, CF_3 , OCF_3 , $\text{NR}^{13}\text{R}^{14}$, $\text{NR}^{13}\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, OH , $\text{C}(\text{O})\text{OR}^{13}$, SH , $\text{SO}_2\text{NR}^{13}\text{R}^{14}$, SO_2R^{13} , $\text{NHC}(\text{O})\text{R}^{13}$, $\text{NHSO}_2\text{NR}^{13}\text{R}^{14}$, $\text{NHSO}_2\text{R}^{13}$, $\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, $\text{C}(\text{O})\text{NR}^{13}\text{OR}^{14}$, $\text{OC}(\text{O})\text{R}^{13}$ and cyano.

223

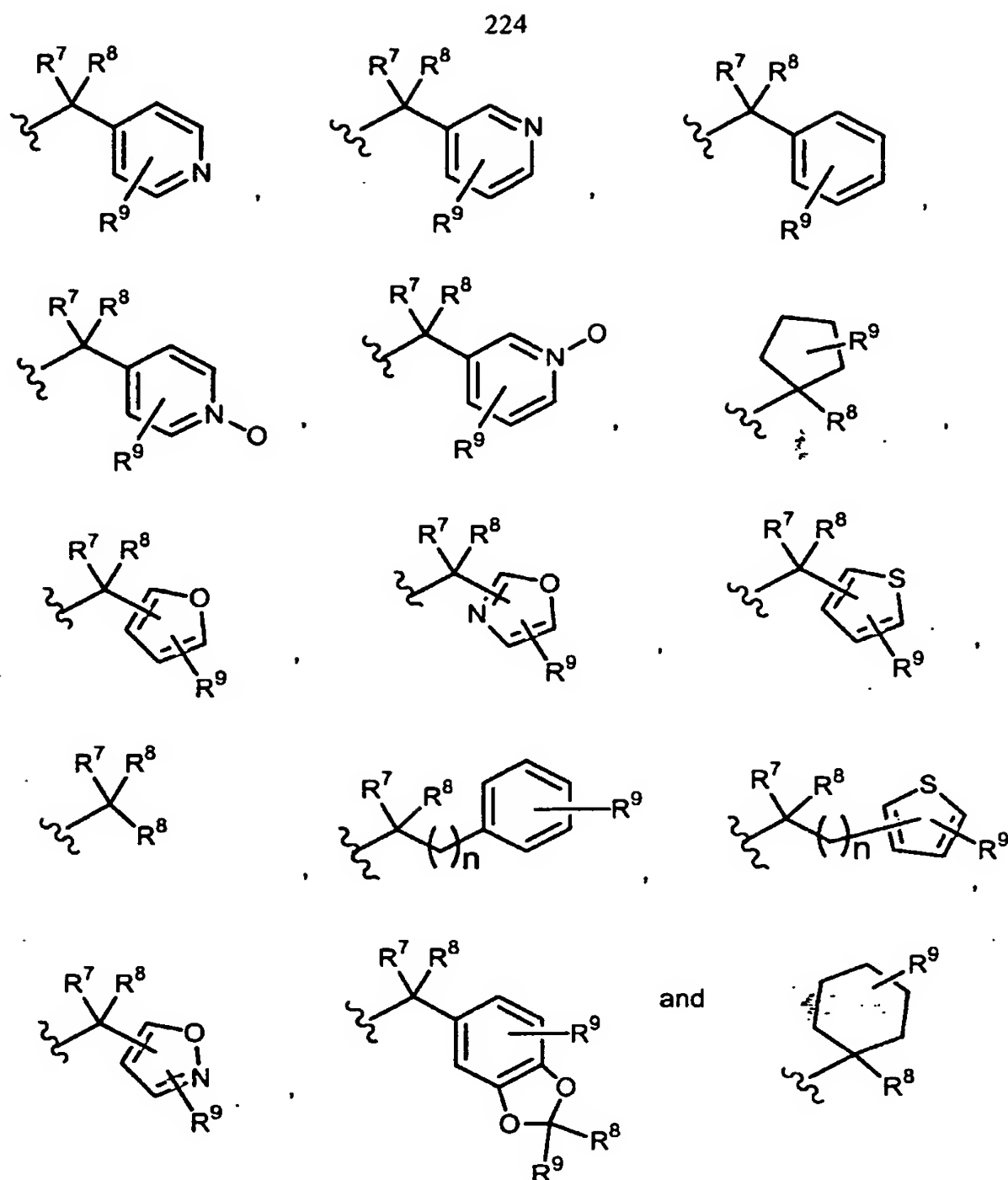
R^{12} is hydrogen, $OC(O)R^{13}$, or an optionally substituted aryl, heteroaryl, arylalkyl, cycloalkyl, alkyl, cycloalkylalkyl or heteroarylalkyl group;

R^{13} and R^{14} are the same or different and are independently selected from the group consisting of H; optionally substituted or unsubstituted alkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, and fluoroalkyl, or R^{13} and R^{14} when taken together form an optionally substituted 3 to 7 membered heterocyclic ring containing one to two heteroatoms selected from O, S and N, and wherein the substituents on the optionally substituted groups are selected from the group consisting of H, alkyl, aryl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, carbonyl and halogen and

t is 1 or 2.

52. The compound of Claim 51 wherein:

A is selected from the group consisting of:



wherein:

R^7 is selected from the group consisting of H, CF_3 , fluoroalkyl, alkyl, cycloalkyl;

5 R^8 is selected from the group consisting of H, alkyl, or fluoroalkyl and

R^9 is selected from the group consisting of: H, F, Cl, Br, CF_3 , alkyl, or fluoroalkyl.

10 53. The use of a compound of any of Claims 1 to 33 for the manufacture of a medicament to treat a disease of any of Claims 35-50.

54. The use of a compound of any of Claims 1 to 33, 51 and 52 for the manufacture of a medicament to treat a disease of any of Claims 35-50.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/32628

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D409/12 C07D405/12 C07D207/44 C07D401/08 C07D403/12
C07D401/12 C07D409/14 C07D417/12 A61K31/4015 A61K31/4025
A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HANAINEH-ABDELNOUR L ET AL: "Some Synthetic Applications of 2,3-Dichloro-N-phenylmaleimide: A Novel Synthesis of 2-Phenylpyrrolo[3,4-b]quinoxaline-1,3-diones. I" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 55, no. 40, 1 October 1999 (1999-10-01), pages 11859-11870, XP004178612 ISSN: 0040-4020 example 3B; table 1 --- -/--	1,51



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

8 document member of the same patent family

Date of the actual completion of the international search

4 February 2003

Date of mailing of the international search report

17/02/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040. Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Seitner, I

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/32628

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TILLACK, ANNEGRET ET AL: "Asymmetric catalysis. IV. Hydrosilylation of acetophenone with pyrrolidine-2,5-dione modified 'Rh(COD)Cl ₂ catalyst" JOURNAL OF ORGANOMETALLIC CHEMISTRY (1994), 482(1-2), 85-91 , XP001109607 examples 14,15 ---	1,51
X	AUGUSTIN, MANFRED ET AL: "Disubstitution in 2,3-dichloromaleimides" ZEITSCHRIFT FUER CHEMIE (1977), 17(6), 215-16 , XP008013330 example 16; table 1 ---	1,51
Y	WO 01 64208 A (SMITHKLINE BEECHAM CORP ;WIDDOWSON KATHERINE L (US); PALOVICH MICH) 7 September 2001 (2001-09-07) example 1 claims 1-5 ---	1,35,38, 51,53,54
Y	WO 00 21927 A (FENWICK ASHLEY EDWARD ;HOLDER JULIE CAROLINE (GB); SMITH DAVID GLY) 20 April 2000 (2000-04-20) example 1; table A page 1, line 8 ---	1,35,38, 51,53,54
Y	DAVIS P D ET AL: "INHIBITORS OF PROTEIN KINASE C 1. 2,3-BISARYLMALEIMIDES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 35, no. 1, 1992, pages 177-184, XP000910195 ISSN: 0022-2623 examples 6,7 column 1 -----	1,35,38, 51,53,54

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/32628

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 35-50 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/32628

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 0164208	A	07-09-2001	AU	3997001 A	12-09-2001
			EP	1261328 A1	04-12-2002
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